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REPORT OF THE CANCER DETECTION CENTER DEMONSTRATION IN MASSACHUSETTS

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SINCE 1910 the movement for periodic health examinations has gained increasing support from life-insurance companies, from health departments, from the medically served industrial groups and from the medical profession in general. One of the early efforts to provide examinations was undertaken in 1919, when a "health clinic" was opened at the Boston Dispensary for the "self-supporting working people."[1] A charge of $5.00 was made for the examination. No treatment was included, and all findings were reported to the subject's physician. After a study of 1000 patients it was concluded that the principle of a routine physical examination, whether made in a clinic or by an individual practitioner, was essential in a preventive-medicine program.

In November, 1922, the John Hancock Mutual Life Insurance Company made arrangements to give its policyholders free physical examinations and diagnostic services for suspected cancer at the Collis P. Huntington Memorial Hospital. All policyholders were circularized with a pamphlet giving certain basic facts about cancer and were urged to use this free diagnostic service.

Many physicians and organizations urged the practice of periodic health examinations, but its adoption was slow. In 1937 a clinic for apparently well women was opened in New York, in conjunction with the Strang Tumor Clinic.[2] During the next year a center was established in Philadelphia for the examination of a group of apparently normal women to determine the value of periodic gynecologic examinations in the prevention and early diagnosis of cancer of the uterus.[3] A total of 1319 women volunteered to be examined twice a year for five years. Since then, so-called cancer detection centers have been established throughout the country. Designed for the examination of symptom-free persons only, such centers vary widely in scope and thoroughness of testing.

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The American Medical Association has approved establishment of these centers, provided that they conform to policies of local county medical societies. In 1946 the American College of Surgeons accepted the American Cancer Society's invitation to assume a supervisory role in relation to the centers, develop a standard for their guidance and publish annually a list of those conforming to the standards of the American College of Surgeons.[4]

Cancer detection centers vary greatly in type and cost of examination and in the percentage of cancer found.

A major question, in the operation of many cancer detection centers, has been: Do results justify the expense? Admittedly, in cancer detection, the cost per case is high.[5, 6] However, many leaders in this field believe that other considerations must be included to achieve a balanced appraisal — that it is unfair to gauge the value of detection centers only by the number of cancer patients found. They point out that cancer-detection clinics are primarily concerned with well persons who may harbor silent malignant lesions offering the greatest opportunity for cure.

Past experience indicates that lack of personnel and facilities would prohibit the examination of all persons who might desire to avail themselves of service through the medium of detection centers — hence the urgent need for general practitioners to offer this type of service to families under their care and to others who may seek this service.

As cancer-detection practices develop in different parts of the country, several deviations from the complete physical examination, — advocated at first, — have been inaugurated experimentally. For example, in some cases the examination has been limited to accessible sites and in other instances examinations were restricted to one sex or to persons over thirty or forty years of age.[2, 3, 5, 7-9]

In a study of cancers discovered at 96 centers, it appeared that the greatest incidence was found in sites ordinarily considered accessible. However, despite attempts to restrict such examinations to persons who could benefit by early detection of cancerous conditions, the purpose of the centers is

partially defeated by long waiting lists and the delay entailed.

Although detection centers were originally intended for examination of symptom-free persons only, many of the centers found a cancer-incidence rate so great that it became apparent that many examinees did not qualify as well persons. Even those subjects denying symptoms of cancer apparently do not represent a cross-section of the population, since reports from various centers suggest that a common reason for seeking examination is the occurrence of cancer in the subjects' families.[3, 5, 7, 10]

The Massachusetts Demonstration

In an attempt to determine the value and need of such clinics, an evaluative study was carried on from May, 1948, to July, 1950, as a joint project of the Cancer Control Unit of the Harvard School of Public Health, the Massachusetts Department of Public Health and the Palmer Unit of the New England Deaconess Hospital. This study was made possible through grants from the National Cancer Institute. The plan of operation was to establish an experimental detection center and to determine its place in a cancer-control program. This included the evaluation of methods of diagnosis most applicable to the detection of cancer in the physician's office and instruction of physicians in these technics, as well as the measurement of the effectiveness of screening by the seven danger signals to determine their value in cancer education.

During the period of operation of the Center, graduate students enrolled in cancer-control courses at the Harvard School of Public Health received individual instruction in the detection technics applicable in private practice as well as in organized detection centers. Various instruments developed for routine use in conjunction with complete physical examination were demonstrated.

At the time of organization of the Palmer Detection Center the policy of screening by means of the seven danger signals was adopted; throughout the period of study emphasis was laid on thoroughness rather than on speed and large numbers. The policy of the Cancer Detection Center was not to replace periodic visits to the family physician but rather to complement his examination by introducing procedures not ordinarily carried out in the average physician's office. No therapy was carried out unless at the request of the family physician.

The examination was closely confined to detection of cancerous and precancerous lesions. A few biopsies of cervixes and of rectal polyps were taken to establish the diagnosis. Supplementary roentgenologic procedures were carried out when the history or clinical findings suggested them. Physical examination of the thorax was limited to the thoracic wall, in the belief that a routine x-ray film was a more accurate method of revealing chest disease than even unhurried auscultation and percussion.

Head and Neck

It was not practicable to record in detail all the minor lesions of the skin found on examination, but all skin lesions of possible clinical significance were recorded.

The eyelids were carefully examined in conjunction with examination of the remainder of the skin surface, but no visual tests were given.

Nasal examination was limited to the use of the speculum, without mucosal shrinking, and to testing of nasal passages for patency by having the individual blow alternately through one nostril and then the other.

The mouth and oropharynx were inspected in all cases. The examination of the larynx with the laryngeal mirror was done routinely by some of the physicians, but not all of them considered themselves qualified by training or experience to make this examination.

Gastrointestinal and Genitourinary Tracts

Routine x-ray studies of the gastrointestinal tract were not carried out, because of lack of facilities for performing a large number of routine procedures in the hospital roentgenologic department and because of the expense involved.

With the knowledge gained from previous clinical experience, routine sigmoidoscopic examinations were made. All the examinees were instructed to take an enema before reporting to the Center, and it was found that the practice was most satisfactory when the enema was taken three or four hours beforehand. An attempt was made in each case to introduce the sigmoidoscope to 25 cm., but frequently a distance of only 16 or 17 cm. was reached.

Routine examination of the stools for occult blood was not performed, as it was considered unreliable because of frequent rectal abrasions after enemas and the possibility of obtaining false positive reactions because of the meat factor in the diet.

Complete urinalysis was performed in all cases, particularly with reference to the presence of blood.

Routine palpation of the prostate gland was included for all men as part of the digital examination of the rectum.

Breast and Pelvis

A meticulous examination of the breasts from the standpoint of inspection and palpation was performed routinely.

The pelvic findings were based on bimanual and speculum examination. A routine vaginal smear was taken for cytologic study, either by the physician in attendance or by the clinic nurse.

At the time appointments were made instructions were given to avoid a vaginal douche before the

examination in order to prevent the destruction of the smear's value by flushing out vaginal secretions.

Laboratory Studies

No serologic tests were performed routinely, but complete blood counts were performed on all examinees, including a red-cell and white-cell count, a hemoglobin determination and a blood-smear study.

Composition of the Group Examined; Reasons for Requesting Examination

A total of 890 persons were examined at the Center, 865 of whom were apparently symptom-free. The remaining 25 had symptoms but were admitted at the beginning of the study. One hundred and eighty-nine other persons with symptoms applied for examination at the Center but were advised to consult their family physician or a diagnostic clinic.

In the total group examined at the Center 32.9 per cent were under the age of forty; 59.8 per cent were between forty and sixty and 7.3 per cent were over sixty years of age.

It was found that all who applied for examination were motivated by one of three reasons: the presence of symptoms, a family history of cancer or a desire for a check-up. The publicity had stressed that only symptom-free persons would be accepted, but despite this fact many calls were received from persons who admitted on questioning that they were not well. Of the group, 30.4 per cent reported that one or both parents had had cancer. A comparison with 843 cancer patients at State cancer hospitals showed that 17.2 per cent of this group had parents with cancer, a much smaller rate than that found in the Detection Center.

Polyps Found Among Symptom-Free Persons

A total of 21 rectal polyps were found, 19 among the symptom-free; 2 subjects gave a history of hysterectomy.

Cancers Found Among Symptom-Free Persons

Five cancers were found among the examinees (Table 1). Three of these cancers were found as the result of the examination at the Detection Center; one was a Grade III carcinoma of the cervix, the second a squamous-cell carcinoma in situ of the cervix and the third a minute focus of carcinoma in situ in a cervical stump. Two other cases were reported at the time of follow-up of the examinees. In one instance the Pathology Department had advised at the time of the detection examination that a biopsied rectal polyp be removed, since it was a "mucosal polyp actively growing"; the patient procrastinated, despite the admonition to act immediately, and after a delay of nine months the growth was excised in a physician's office; on biopsy the growth was found to contain a minute focus of carcinoma. In another case no evidence of cancer was found during examination, but a year later an exploratory laparotomy showed carcinoma of the pancreas with metastases to the liver.

Persons Not Accepted at Center but Examined at Palmer Diagnostic Clinic

One hundred and eighty-nine persons were not accepted for examination at the Detection Center because of the presence of one or more of the cancer danger signals. One hundred and thirty-one of these, 38 males and 93 females, later visited the Palmer Diagnostic Clinic. The average age of the males was 3.9 years more than that of those who were examined in the Detection Center, and the average age of the females was 3.2 years more. Thirteen of this group examined at the Palmer Diagnostic Clinic were found to have cancer.

TABLE 1. *Incidence of Cancer.*

Symptom-free persons examined at the Center:	
Cancer found at Center	3*
Cancer found after Center visit and reported at follow-up	2
No cancer found at Center or reported at follow-up	848†
Follow-up not completed (1 male, 11 females)	12
Persons with danger signals examined at the Center:	
No cancer found at Center or reported at follow-up	25‡
Total number examined	890
Persons with danger signals not accepted for examination at the Center:	
Cancer found on examination elsewhere	13
Presence of cancer undetermined	1
No cancer found	160
Follow-up not completed	15
Total	189

*One had a history of a supravaginal hysterectomy.
†Seventy-five had a history of a supravaginal or panhysterectomy.
‡Three had a history of a supravaginal or panhysterectomy.

Of the persons who admitted that they had sores that would not heal 21.0 (± 9.4) per cent were found to have cancer; of those with a painless lump or thickening 8.5 (± 3.7) per cent had cancer; and of those with irregular bleeding or discharge 10.0 (± 4.6) per cent had cancer.

Apportionment of Time Required for Various Phases of the Examination

A time study was made for each procedure at the Center. The average time spent by a physician in examining each subject was 68.6 minutes; 46.8 of these minutes were spent in taking the medical history and in performing the various examinations. An average of 12.7 minutes was spent in filling out forms. In addition, 9.1 minutes were spent in dictating letters on the findings, which was done after all laboratory reports had been received.

The Center secretary made the appointments, screened the applicants, filled out the first history form, prepared all forms with identifying data, transcribed the physicians' dictation from dicta-

phone records and assembled the complete record of each patient. The various procedures averaged 61.2 minutes per patient.

An average of 28.2 minutes per patient was spent by the nurses and technicians in collecting the blood, urine and vaginal-smear specimens and in taking x-ray films.

The total time spent by the Center personnel on each examinee was two hours and thirty-eight minutes.

Publicity

The publicity of the Center was limited in scope in order to keep the Center from becoming overtaxed and because it was desired to avoid the possible impression of a free service.

Letters to Family Physicians

It was the policy of the Center to send a letter to the family physician either summarizing the findings or reporting that the examination was negative. However, 393 patients either did not have a family physician or preferred not to have a report sent to the physician. It is thought that some persons wished to spare the feelings of the family physician by keeping from him the fact that they had been examined at the Center. Of the group of 393, 112 were apparently normal; the remaining 281 had some conditions that warranted attention. Many of the conditions were slight — as, for example, epidermophytosis, ill-fitting dentures and so forth.

Follow-up of Examinees

A follow-up was attempted on all persons who applied for examination at the Center, both on those accepted for examination and on those who were rejected because of the presence of danger signals.

If an abnormal condition had been found during the examination at the Center, a follow-up letter was sent to the examinee to ascertain whether the recommendations of the examining physician had been followed. If a reply was not received, a worker from the Center visited the subject to determine whether a definite diagnosis had been established. If it was known definitely that a physician or diagnostic clinic had been consulted, the worker obtained the data directly from this source.

One hundred and one recommendations for treatment were made by the examining physicians at the Center. After a median interval of 7.4 months, 60 persons were known to have undergone treatment; this included 8 hysterectomies. Additional operations may have been performed since the follow-up was completed.

The Use of the Seven Cancer Danger Signals in Screening

Of 865 symptom-free persons examined at the Detection Center, 3 were found to have cancer, and out of a total of 853 examinees who were followed 2 others were found to have cancer within the following year, the rate being 3.5 (± 1.6) per 1000. If the 2 additional cases are considered the rate is 5.9 (± 1.7).

Among the subjects with symptoms who were examined at the Palmer Diagnostic Clinic, 13 cancers were found, a crude rate per 1000 of 65.7 (± 17.6). These included 25 who were examined at the Center, 131 examined in the diagnostic tumor clinic at the Palmer Hospital and 42 examined elsewhere — a total of 198. There was a significant difference between the rates for persons with and without symptoms. Those in the group examined at the Palmer Diagnostic Clinic were slightly over three years older than those examined at the Detection Center, but, taking into account some increase in rate due to the difference in age, those with symptoms had a considerably higher rate than those who were symptom-free.

The small number of cancer cases found at the Detection Center, together with the two additional ones discovered at the follow-up, were of special interest. We do not know whether the second of the additional cases represents cancer developing after the examination or whether it was present but not clinically detectable at the time the subject came to the Center.

In the New York detection centers[11] the cancer rate was found to be 3.9 per thousand, a figure similar to that observed at the Palmer Detection Center. In other parts of the country, rates as high as 8.1 per thousand have been reported.[9] Presumably a policy of adhering to the examination of symptom-free persons was not strictly observed in these centers.

Deductions Drawn from the Experience of the Palmer Detection Center

Two years of experience at this Detection Center have yielded factual data and resulted in the formulation of certain opinions concerning such centers.

The physical examination should consist of inspection of the body, including the skin, eyes, ears, nose, mouth, throat, abdomen, extremities and genitalia; palpation of the neck, breasts and abdomen and examination of the female pelvic organs bimanually and by speculum; examination of a vaginal smear; examination of the rectum, including palpation of the prostate gland in male patients; sigmoidoscopy; and roentgenography of the chest. Sigmoidoscopy is one of the most important parts of the examination, and is too often omitted by the general practitioner.

Examination of the stools for occult blood may be a useful additional procedure. However, the results of the examination would require careful evaluation to avoid assigning importance to possible false positive reports.

It was believed that the examination of the larynx could be omitted in symptom-free persons, as it seems extremely unlikely that any tumors or

precancerous lesions would be discovered in a routine examination of the larynx in patients without symptoms of hoarseness, soreness or difficulty in swallowing.

Although routine serologic tests for syphilis were not made, they may be fully justified in any cancer detection-prevention program, on the basis of certain studies[12] that indicate an association of selected precancerous lesions with syphilis. A complete blood examination, with the possible exception of a differential white-blood-cell count, seems justified.

Many of the persons seen at cancer-detection centers give a family history of cancer.

The majority who apply for this type of examination are able to pay at least a part of the cost.

A complete examination and recording of data should take a physician and the clinic secretary about an hour each and the nurses and technicians about half an hour, a total of approximately two and a half hours per patient. The patients would spend about one hour and a half at the clinic.

The cost of a routine examination as performed at the Palmer Center was about $25.00 per patient.

The number of cancers found among asymptomatic subjects was small. It would have been greatly increased if applicants with symptoms had been accepted at the Center. Obviously the place for the examination of persons with symptoms is the private physician's office or a cancer-diagnosis clinic, rather than a detection center. The few cancers that are found among asymptomatic persons, as well as the high cost of each examination, preclude large-scale financing of cancer-detection centers by either governmental or voluntary agencies. Moreover, it is probable that many of the procedures carried out at the detection center could be done by the general practitioner if proper instruments were available to him at a reasonable cost and if he were willing to spend at least one hour in taking the history and making the examination.

Arrangements for special procedures such as roentgenograms of the chest might be made at the various larger hospitals so that practitioners might send their patients to the hospitals for these examinations at a nominal cost, or the official health agencies might furnish or underwrite these special services.

Consideration has been given to the following: whether or not the physical examination can be divided between the physician's office and the Detection Center, the Center furnishing supplementary diagnostic procedures that are not carried out by the physician; the evaluation of methods most applicable to the detection of cancer in the physician's office; and a practical method of instructing physicians in selected detection technics.

It is assumed that a well-trained practicing physician can perform all the procedures that are utilized in the Cancer Detection Center — and that these procedures are not generally used in practice by physicians at the present time.

The motion pictures currently being shown under the auspices of county medical societies in co-operation with the State Divisions of the American Cancer Society and the official health agencies should do much to improve the physician's technic in examination of the breast. Every effort should be made to emphasize the practical aspects of early detection of cancer through the medium of technical motion pictures of this nature. These films should be shown frequently to professional audiences in general and to every county medical society in particular. Many physicians do not perform routine pelvic examinations, although this procedure should be an integral part of the periodic health inspection of every female. Although there is an observed improvement in the diligence with which pelvic examinations are performed in actual medical practice by recent graduates, it is still difficult to persuade many of the older general practitioners to improve their method of pelvic examination and to apply it consistently.

It is our belief that the most important part of a complete health inspection, — and a part not at present routinely carried out by the general practitioner, — is the rectal examination; this should include a digital examination and sigmoidoscopy.

In our opinion, any of the technics used at a Detection Center can be used by the general practitioner if his interest is sufficiently aroused and if proper instruments are available for his office use.

Facilities for making chest films might be made accessible at the various hospitals to enable practitioners to send patients for routine x-ray examination at a nominal cost; this also applies to other laboratory procedures.

State medical societies can do much to stimulate continued improvement in the quality and the thoroughness with which cancer-detection practices are carried on by members of their component county societies. Such a program would call for careful planning of postgraduate education and a fuller utilization of the educational media.

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ADRENOCORTICAL FUNCTION IN PERNICIOUS ANEMIA*

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THOMAS ADDISON'S clinical description of "idiopathic" anemia reveals so many manifestations identical to those encountered by him in disease of the suprarenal capsules[1] that his failure to differentiate the two disorders clearly in his preliminary report in 1849[2] can readily be understood. That temporary adrenal insufficiency might be present in pernicious anemia in relapse was suggested a decade ago by the observations of Strauss and Fox,[3] who noted: ". . .this behavior with regard to water and sodium exhibited by patients with Addisonian pernicious anemia is not unlike that shown by patients with Addison's disease of the suprarenal capsules."

The purpose of this communication is to bring together certain of the available data pertinent to this problem and to present limited observations concerning ketosteroid excretion and eosinophil response to adrenocorticotrophic hormone in patients with pernicious anemia.

CLINICAL OBSERVATIONS

Among the manifestations of Addison's disease of the suprarenal capsules[4-7] that may occur in Addisonian pernicious anemia in relapse but appear to be relatively uncommon in other forms of anemia are: asthenia; arterial hypotension; pigmentation of skin and mucous membranes; anorexia, nausea, vomiting, diarrhea; apathy and other mental changes; inability to conserve sodium chloride; inability rapidly to excrete a water load; nocturnal polyuria and fixation of urinary specific gravity; diminished glomerular filtration and elevation of serum nonprotein nitrogen; flat oral glucose-tolerance curve; absence of fall in number of circulating eosinophils after injection of adrenocorticotrophic hormone; and diminished urinary excretion of 17-ketosteroids.

The occurrence of these manifestations in Addison's disease is discussed in recent articles by Loeb,[4] Soffer,[5] Sorkin[6] and Thorn and Forsham[7] and need not be further documented here. Data concerning their occurrence in pernicious anemia in relapse follow.

Asthenia

"It makes its approach in so slow and insidious a manner that the patient can hardly fix a date to his earliest feeling of that languor which is shortly to become so extreme."[1] This statement by Addison so well describes the situation observed during relapse in pernicious anemia that it is often quoted,[8, 9] either directly or in paraphrase, by students of this disease. That the weakness is not due solely to the anemia is evidenced by the fact that many patients exhibit striking improvement within forty-eight hours after the initiation of liver-extract or vitamin B_{12} therapy and long before significant rises in hemoglobin or red-cell levels have occurred.[8, 10] Furthermore, the asthenia is often far greater than that observed in hypochromic anemia at comparable hemoglobin levels. Cabot[11] comments repeatedly on the lack of correlation between the weakness and other general symptoms and the degree of anemia.

Arterial Hypotension

". . .the pulse, perhaps large, but remarkably soft and compressible . . ." (Addison[1]). "The blood pressure is very low; indeed there are few diseases in which low records have been so often found. Readings of 60 and 80 mm. of mercury for the systolic pressure are not unusual" (Cabot[11]). "The blood pressure is usually low" (Minot[12]). Lerman and Means[13] in 1928 reviewed the literature on blood-pressure readings in pernicious anemia and analyzed 500 cases from the Massachusetts General and Peter Bent Brigham hospitals. They agreed with previous authors that there was an increased frequency of hypotension in patients with pernicious anemia; they noted only one undoubted case of hypertension among their 500 patients. In contrast is the fairly common finding of arterial hypertension among patients with anemia due to diverse factors, although, to be sure, the blood pressure tends to fall in the presence of any severe anemia.[14]

Pigmentation of the Skin and Mucous Membranes

Castle and Minot[15] noted that a brownish color of the skin is apt to be found on the exposed parts of the body and mucosa of the mouth in patients with pernicious anemia and that vitiligo is not rare, often being combined with brownish pigmentation. Minot and Murphy[16] observed that skin pigmentation disappeared after liver therapy. Cabot[11] and Wintrobe[9] have commented on the occurrence of both skin pigmentation and vitiligo. The latter was noted by Addison in adrenal disease[1] and is said to occur in about 7 per cent of patients.[4, 6] It is of interest that Kracke,[17] in regard to pernicious anemia, has commented on ". . .irregular blotchy areas of brown pigmentation. This. . . finding, with low blood

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pressure and extreme weakness, might easily be confused with Addison's disease."

Anorexia, Nausea, Vomiting and Diarrhea

The occurrence of anorexia in pernicious anemia and the return of appetite in remission is so well known that comment is superfluous. Addison[1] stated: "The appetite fails." Indeed, Castle, Heath and Strauss[18] in 1931 suggested that fluctuations in appetite and hence in food ingestion played an important role in "spontaneous" remissions and relapses. In 1935 Minot[19] commented on the fact that one third of patients with pernicious anemia present gastrointestinal symptoms such as indigestion, nausea, vomiting and diarrhea as the predominant manifestations of the onset of the disorder. Since these disappear with treatment, with no change in gastric anacidity, it is apparent that they do not stem from a lack of free hydrochloric acid, and since they subside after treatment before significant blood changes occur, it is apparent that they are not due to anemia per se. Furthermore, they are not characteristic of other types of anemia.

Apathy

"The patient can no longer rise from his bed, the mind occasionally wanders, he falls into a prostrate and half-torpid state and at length expires" (Addison[1]). All those who have had experience with any number of patients suffering from pernicious anemia in relapse have been impressed with the apathetic, almost stuporous patient seen on admission, often disoriented, who within twenty-four to forty-eight hours after treatment is alert and mentally clear. It is of interest that Sturgis[20] noted the occurrence of mild depression, memory disturbances and irritability in approximately 60 per cent of patients with pernicious anemia, which may be compared to the incidence of 70 per cent in Addison's disease.[6] Again it may be noted that these phenomena are not notable in patients with severe anemia due to chronic blood loss.

Inability to Conserve Sodium Chloride

Strauss and Fox[3] in 1940 noted that 2 patients with pernicious anemia in relapse actually lost weight (presumably body water) while receiving large doses of sodium by mouth and that a third showed no significant gain, although all 3 retained water (and presumably sodium) when receiving large amounts after specific therapy. This was in striking contrast to the excessive retention of salt and water observed in patients with other types of anemia, in whom the magnitude of retention was directly correlated with the severity of the anemia. Vaughan[21] in 1931 studied weight changes following therapy in patients with pernicious anemia who were receiving a strict basal diet containing only 25 calories per kg. of body weight. She noted gains of up to 3.3 kg. between the initiation of treatment and the height of the reticulocyte response (generally a period of approximately one week) — gains that could be ascribed only to the retention of water (and presumably sodium), suggesting that therapy in some way influenced the patients' salt and water metabolism.

Inability to Excrete Water Rapidly

This phenomenon, which is the basis of the Robinson–Power–Kepler water test described in 1941[22] for adrenal insufficiency, resides in the inability of the patient with Addison's disease to exhibit the usual diuresis after drinking water. Meulengracht, Iverson and Nakazawa[23] in 1928 reported the results of 96 water-loading tests in 35 patients with pernicious anemia. One liter of water was given at 8 a.m. without prior preparation of the patient; hourly urine collections were made until noon. With patients in relapse the four-hour volume was generally under 200 cc. After remission increasing ability to excrete water rapidly was observed. In contrast to these results in pernicious anemia, entirely normal water excretion was shown in 11 patients with anemia due to blood loss.

Nocturnal Polyuria and Fixation of Specific Gravity

Christian in 1916[24] noted that 13 of 14 patients with pernicious anemia exhibited nocturnal polyuria together with fixation of specific gravity, which in 10 of the patients was below 1020. Saltzman[25] and Essen and Porges[26] are quoted by Meulengracht and others[23] as making similar observations; Stieglitz[27] in 1924 corroborated this finding in 6 additional cases. These phenomena are not reported in other types of anemia.[23]

Diminished Glomerular Filtration and Elevation of Nonprotein Nitrogenous Components of the Serum

Fouts and Helmer[28] in 1938 found that 39 of 50 patients with pernicious anemia in relapse had less than 75 per cent of normal urea clearance, with increased clearance rates following remission in most cases. Gettler and Lindemann[29] studied 32 patients with pernicious anemia in 1920 (before the days of liver therapy). Twenty-one exhibited blood nonprotein-nitrogen levels of 40 to 108 mg. per 100 cc.; in 7 cases it was 60 mg. per 100 cc. or higher. Urea-nitrogen levels above 15 mg. per 100 cc. were noted in 18 patients; 15 had creatinine levels above 1.5 mg. per 100 cc.

Bradley and Bradley[30] found diminished glomerular-filtration rates in 2 patients with uncomplicated pernicious anemia and normal rates in 2 others, in one of whom the rate fell significantly as the hematocrit rose. Of 3 patients with pernicious anemia and vascular disease 1 had a normal filtration rate, as did a patient with pernicious anemia and diabetes. A lack of correlation between hematocrit levels and filtration rate was also noted in 7 patients with various types of anemia.

Flat Oral-Glucose-Tolerance Curves

Groen[31] in 1938 noted that the blood sugar failed to show the usual rise after the instillation of glucose into the small intestine of patients with pernicious anemia in relapse; he demonstrated that this was due to poor absorption from the bowel. After specific treatment normal absorption occurred. Such observations have not been reported in anemia due to blood loss. In Addison's disease the blood glucose fails to show a normal rise after the oral administration of this sugar, but, as Thorn and others[32] have shown, it reaches normal heights after intravenous administration.

Absence of Fall in Circulating Eosinophils after Injection of Adrenocorticotrophic Hormone

Thorn and others[33] first noted in 1948 that in normal subjects and patients with miscellaneous ailments the injection of 25 mg. of ACTH was followed within four hours by a significant decline in the level of circulating eosinophils, generally to more than 50 per cent lower than their original level. In contrast, in patients with Addison's disease no significant change in eosinophils occurred. Although these workers state that if the level of circulating eosinophils does not fall a complete absence of adrenal-cortical reserve may be assumed, it appears that this is not as definitive a test as they believed.

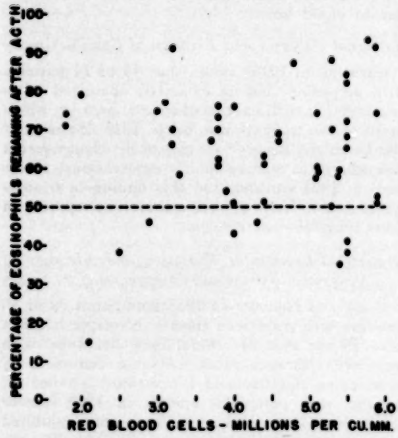

FIGURE 1. *Percentage of Circulating Eosinophils Remaining Four Hours After the Injection of 25 Mg. of ACTH.*

Eosinophil counts have been made (before and four hours after the injection of a single dose of 25 mg. of ACTH) 53 times in 7 patients in whom the diagnosis of pernicious anemia was established. In Figure 1 the number of eosinophils remaining has been plotted as the percentage of the original number, with the red-cell count as abscissa. It is apparent that the fall in eosinophils was greater than 50 per cent in only 8 of 53 such tests. The lack of correlation between the decline in number of eosinophils and the red-cell level is apparent. Three additional patients (2 in remission, 1 in relapse) have been similarly tested since this manuscript was prepared. In none did the eosinophils show a significant fall.

In contrast to these findings are observations on 5 patients with hypochromic anemia due to blood loss whose eosinophil counts fell to 41, 41, 35, 32 and 12 per cent of their initial number four hours after ACTH administration.

In order to test the hypothesis that the absence of a fall in eosinophil level was the result of inadequate stimulation of the adrenal cortex from a single intramuscular dose of ACTH, 5 patients in remission who had showed no significant declines in eosinophil levels after single doses of 25 mg. of ACTH received 25 mg. every six hours for four to five days. Their eosinophil counts, made on the day ACTH was commenced and daily thereafter, were respectively: 83, 135, 145, 146, 135, 166; 179, 213, 196, 199, 114, 197; 246, 273, 282, 306, 344; 404, 407, 345, 284, 184, 276; and 193, 88, 16, 27, 34. Thus, only in the last patient did the expected eosinopenia occur. In the fourth patient a moderate decline may be noted.

Two of these patients who had not developed eosinopenia after five days of intramuscular ACTH therapy received 20 mg. administered in a slow intravenous infusion over a period of twenty-four hours.[34] Their eosinophil counts, which were 479 and 276 per cu. mm. before infusion, fell to 6 and 4 per cu. mm. at the conclusion of the infusion.

Since the lack of eosinopenia after ACTH administration in these patients might possibly be due to some peculiarity in their eosinophils, 3 patients who did not respond to ACTH were given cortisone (Cortone, Merck) by mouth. One received 100 mg. at 8 a.m. and noon. His eosinophil count (214 per cu. mm. at 8 a.m.) had fallen to 9 per cu. mm. by 2 p.m. The second patient, whose eosinophil count was 196 per cu. mm. before cortisone, fell to 3 per cu. mm. after he had received 200 mg. daily for two and a half days — a total of 500 mg. The third patient's eosinophil count fell from 303 to 11 per cu. mm. twenty-four hours after cortisone was initiated in doses of 100 mg. every six hours by mouth.

In this connection it is of some interest that eosinophilia was common in pernicious anemia in the days before the advent of liver therapy.[35]

Diminished Urinary Excretion of 17-Ketosteroids

Normally above 8 mg. per twenty-four hours in males, the urinary excretion of these steroids, which are presumed to derive from both the adrenal cortex and the male gonads, is usually below 5 mg. in patients with Addison's disease. In 3 male patients with pernicious anemia the twenty-four-hour excretion prior to vitamin B_{12} therapy was 2.4, 4.8 and 5.7 mg. The excretion was recorded as 3.2, 6.9 and 8.4 mg. respectively, within two to three weeks after the initiation of vitamin B_{12} therapy. In 2 other male patients who received 25 mg. of ACTH every six hours for five days, the twenty-four-hour excretion was 6.8 and 7.6 mg. Depression of 17-ketosteroid excretion has been reported in other types of anemia.[36]

Discussion

A number of manifestations reported in Addison's disease have not been observed in pernicious anemia. The fasting blood-sugar level, frequently low in adrenal disease, has been found at the upper range of normal in untreated pernicious anemia.[37] The basal metabolic rate, often lowered in primary destruction of the adrenal cortices, is more often normal or slightly elevated in pernicious anemia.[38]

Crises, with severe disturbances in serum-electrolyte levels, have not come to our attention in pernicious anemia. However, measurement of serum electrolyte was relatively rare prior to the advent of liver treatment for pernicious anemia, and mortality under observation in untreated cases is equally rare today. What caused the fatal outcome in pernicious anemia in the pre-liver-treatment days is not altogether clear. It seems, despite the fact that repeated transfusions could maintain the hemoglobin at a level at which anemia *per se* was not lethal, that these patients died in a state of extreme exhaustion.

Although Addison commented on the maintenance of body weight in "idiopathic" anemia in contrast to the wasting in adrenal disease (and most writers adhere to this concept), Jones,[39] who made a careful analysis of weight changes in pernicious anemia, found that 42 of 44 patients lost from 2 to 42 per cent of body weight in relapse; this finding tends to negate the belief that nutrition is not impaired.

Thorn and others[22] have noted that the ratio of uric acid to creatinine in the urine rises after adrenocortical stimulation by ACTH, resulting in an increased excretion of uric acid that presumably is not due to increased glomerular filtration. The rise in excretion of endogenous uric acid noted by Riddle[40] after the institution of specific therapy in pernicious anemia may reasonably be ascribed to the destruction of large numbers of red-cell nuclei that accompanies the rapid maturation of red blood cells.

The data presented above indicate that a number of manifestations of Addison's disease of the suprarenal capsules may be encountered in patients who have pernicious anemia, whereas they are less often seen in patients with comparable degrees of anemia due to blood loss.

That vitamin B_{12} is a material of importance in the metabolism of essential constituents of cellular nuclei has been suggested by many recent studies.[41] Accordingly, it seems possible that a deficiency of this substance leads to functional impairment of the adrenal cortex or the anterior lobe of the pituitary gland, either as a result of the general "debilitating" effect of the deficiency or because vitamin B_{12} is actually necessary for their proper function. That the adrenal rather than the pituitary gland is involved is suggested by the failure of prolonged ACTH administration regularly to induce eosinopenia.[42] The fact that even after remission of pernicious anemia had been well established 4 of 5 patients so tested failed to respond with significant eosinopenia to the intramuscular injection of 25 mg. of ACTH every six hours for four to five days suggests either continued adrenal unresponsiveness or a tissue factor capable of inactivating intramuscularly administered ACTH.[24] It is nevertheless of interest that Gassner and others[43] have commented on the similarity between the manifestations of vitamin B_{12} deficiency in the cockerel and those of early hypophysectomy in this species. The significance of the observation of Gaines and Broquist[44] that cortisone acetate will support the growth of *S. faecalis R* in the absence of pteroylglutamic acid and of *Leuconostoc citrovorum* 8081 in the absence of citrovorum factor is not yet clear.

The observation (made on adrenal-cortex slices in vitro[45]) that glutathione appears to inhibit the production of cortisone from desoxycorticosterone is of interest in view of the reported high cellular glutathione levels in pernicious anemia.[46] In this connection the suggestion that homocystine cannot be methylated to methionine in the chick when vitamin B_{12} deficiency is present[47] is of further interest, as presumably the cysteine of glutathione is in part derived from cystine.[48]

If the method of Nelson and Samuels (as yet unpublished) proves satisfactory for the assay of the level of 17-hydroxycorticosteroids in the peripheral blood of human subjects, and if this level can be correlated with adrenocortical function, as appears to be the case as noted in their recent report,[49] it should be a relatively simple matter to ascertain whether or not adrenocortical function is in fact diminished in Addisonian pernicious anemia in relapse.

Should it be determined that vitamin B_{12} is necessary for proper adrenal function, the possibility arises that a metabolic antagonist to vitamin B_{12} would be capable of inducing adrenocortical insufficiency. The idea of producing such a state as

a therapeutic procedure in serious hypertensive and other disorders by such means is intriguing; if found to be beneficial it would presumably be much less hazardous than the present method of surgical extirpation of the adrenal glands.[50]

Conclusion

The occurrence of numerous manifestations of Addison's disease of the suprarenal capsule in Addisonian pernicious anemia in relapse suggests that functional adrenocortical insufficiency may be present in certain cases of this condition.

We are indebted to Drs. David S. Citron and Stuart C. Finch for observations made on patients under their care.

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SEVERE HEMORRHAGE DUE TO TROMEXAN*

Report of Three Cases

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TROMEXAN, a new anticoagulant, has recently been accepted for general use. Chemically, it is described as ethyl biscoumacetate (3,3′ carboxymethylenebis-[4-hydroxycoumarin] ethyl ester). It is most widely recognized as "Tromexan" but is also known as "Pelentan," "B.O.E.A." and "D.E.A."

Dicumarol[1] and Tromexan[2] are related members of the coumarin series of drugs. Each is presumed to act in similar fashion, by interfering with the normal production of prothrombin by the liver. The exact mode of action is as yet unknown.[3, 4] The possibility of hemorrhage after Dicumarol administration is well known, and precautions for its use have been repeatedly stressed.[5-7]

Utilizing an aniline-dye test on serum and urine, von Kaulla and Pulver have shown that Tromexan is more rapidly absorbed than Dicumarol in rabbits. This property is thought to be due to the weakening of the methylene linkage between the coumarin groups created by adding the carboxyl radical, which is supposed to allow easier splitting of the coumarin molecules. In human subjects given 900 mg. of Tromexan, the maximum serum concentration occurred in three to six hours. None could be found in the serum after twenty-four hours, but minute amounts of Dicumarol were found to persist as long as a week in similar tests.[8, 9]

There is a lag between the peak serum concentration and the prothrombin time. After a single dose of 1500 mg. of Tromexan Burke and Wright reported a prothrombin time of twenty to thirty seconds at the end of twenty-four hours.

Barker, Estes and Mann report similar experiences with initial doses of 1200 and 1500 mg. Six of their patients had prothrombin times within the therapeutic range, — that is, twenty-seven to fifty-eight seconds, — in sixteen to twenty-four hours.[10]

A similar rapid fall to normal in the prothrombin time, usually within forty-eight to sixty hours, was observed both by Burke and Wright[2] and by Barker and his associates.[10] This property of rapid absorption and excretion is credited with the extra margin of safety that Tromexan possesses in comparison with Dicumarol.

Advertisements in various medical journals state that Tromexan has proved singularly free from the dangers of hemorrhagic complications. We wish to report three instances of serious hemorrhage following the use of Tromexan in a series of 125 patients.

Two of these patients, — one with acute pulmonary infarction, the other with an acute coronary-artery occlusion and myocardial infarction, — had nearly fatal hemorrhages. The third patient had rheumatic heart disease, mitral stenosis, auricular fibrillation and multiple emboli. He died after gross hematuria and a subarachnoid hemorrhage. It is believed that Tromexan was a contributing cause of his death.

CASE REPORTS

CASE 1. C. R., an 82-year-old woman, was admitted to the hospital on April 12, 1950, for removal of a cataract from her right eye. Preoperative examination disclosed a blood pressure of 210/88 and a cardiac rhythm marked by frequent premature beats. There was evidence of generalized arteriosclerosis but no signs of congestive heart failure. An electrocardiogram was normal. On April 14 an intracapsular cataract extraction with iridectomy was performed. On April 17 and 29 two further operations were necessary because of iris prolapse. The sutures were removed on May 8, and the patient's condition was reported as satisfactory.

On May 9 the patient had a "bad" night. She disclaimed any pain but had been sweating and cold all the previous day. Two blood-pressure recordings made at 5 a.m. were 70/60 and 88/40. The respirations were 30; bradycardia and gallop rhythm were present, with moist rales in the dependent lung. An electrocardiogram made that morning disclosed an A-V nodal rhythm, a prolonged QT interval and inverted T waves in leads V_2, V_5 and V_6. A diagnosis of acute anteroseptal myocardial infarction was made, and the patient was transferred to the Cardio-Respiratory Division.

Examination of the blood revealed a hemoglobin of 14.7 gm., a red-cell count of 4,470,000 and a white-cell count of 18,850, with 79 per cent neutrophils, 16 per cent lymphocytes and 5 per cent monocytes; the hematocrit was 50. Urinalysis revealed a specific gravity of 1.022, an acid reaction, ++ albumin and ++++ leukocytes. The blood nonprotein nitrogen was 74 mg. per 100 cc.

Treatment was begun with Heparin, given intravenously every 4 hours, as indicated by the Lee–White clotting time. The initial prothrombin time was fifteen seconds by the one-stage Quick test.[11] Figure 1 indicates the daily prothrombin level and the amount of Tromexan used. Heparin was discontinued on May 12, 10 days prior to the beginning of any hemorrhage.

At 5:55 a.m. on May 22, the patient voided 100 cc. of grossly bloody urine and vomited 5 to 10 cc. of bright-red, mucus-containing clots. The blood pressure was 78/52, the pulse was 88 and regular; the chest was clear. Some clots were seen in the pharynx; these were associated with a small epistaxis reported a few hours previously. At 9:40 a.m. the blood pressure was 86/56. Diet was restricted to fluids. Two dark, bloody stools were passed at 11:10 a.m.

A 500-cc. whole-blood transfusion was begun at once. By 2:45 p.m. the blood pressure was 110/60 and the patient was quiet. On May 23 she received 500 cc. of blood. The hemoglobin that day fell to 8.8 gm. Rectal bleeding continued unabated, with large, bloody stools being passed. On May 24, the hemoglobin was 7.4 gm. and an additional 500 cc. of whole blood was given.

By 5 a.m. on May 25 the blood pressure had dropped to 72/56. The patient continued to pass tarry stools, mixed with bright blood. Twenty minutes later the blood pressure was

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60/34. Plasma transfusion was begun at once, as whole blood was not immediately available. Whole blood was substituted for plasma at 6:30 a.m. By 7:50 a.m. the blood pressure was 84/50. By 9:30 a.m. the blood pressure had risen to 110/84. The patient's color was fair. Hyperpnea was not present. The chest was free of rales; the cardiac rate was regular (84 per minute). The abdomen was soft.

Other measures aimed at controlling the hemorrhage included the use of Hykinone, a water-soluble, synthetic form of vitamin K; vitamin C; and Rutin. These were begun at 9:45 a.m. on May 25 and were continued until May 30. The dose of Hykinone was 72 mg. every 6 hours, given intravenously. Two hundred mg. of vitamin C was given daily, intravenously; 60 mg. of Rutin was given by mouth three times a day.

By May 26 the hemorrhage had stopped. The hemoglobin was 7.8 gm. The blood pressure had stabilized at 104/48. The patient was fed a soft diet and by May 27 had begun to improve. She had no further hemorrhage and was discharged on June 18, 1950.

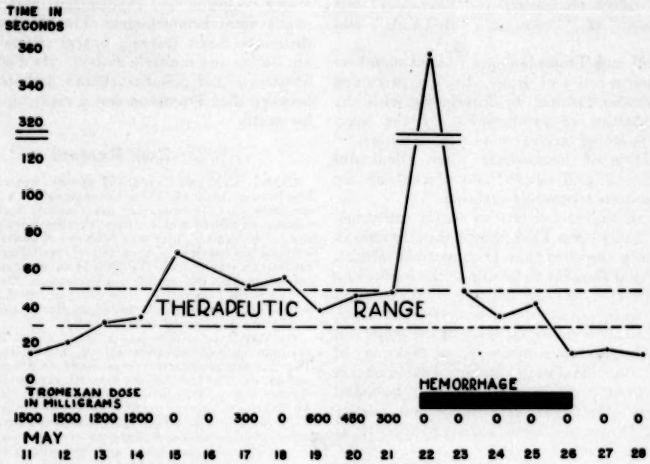

FIGURE 1. *Prothrombin Levels and Tromexan Dosage in Case 1.*

CASE 2. M. Z., a 57-year-old man, had been seen at this hospital in March, 1948, because of an acute coronary-artery occlusion with anteroseptal myocardial infarction. During that admission he was a member of the control group in a Dicumarol study being made at that time[7] and hence did not receive anticoagulants. He returned to his work late in June, 1948.

His second admission followed in March, 1949, because of congestive heart failure due to arteriosclerotic heart disease. He responded well to therapy and was discharged in 10 days. He returned to work early in May, 1949, and was maintained on digitalis, occasional mercurial diuretics and salt restriction. He continued to have occasional exertional angina pectoris, relieved by resting. After a visit on August 19, 1949, he was not seen for seven months.

Shortness of breath was his complaint when he entered the Emergency Room on March 16, 1950. The patient had discontinued all medications, including digitalis. The admitting physician found severe dyspnea, moderate cyanosis, a regular pulse of 110 and respirations of 40. The neck veins were slightly distended. The chest was filled with moist rales, squeaks and wheezes. The blood pressure was 125/100. The heart sounds were obscured by rhonchi. The liver was tender and palpable 8 cm. below the ribs. Moderate ankle edema was present. There was tenderness in the left calf.

Admission diagnoses included arteriosclerotic heart disease, congestive heart failure, probable thrombophlebitis of the left calf and probable pulmonary infarct. Treatment was begun with intravenous lanatoside C, continuous oxygen (by tent), mercurial diuretics, morphine and bed rest.

Laboratory studies of the blood revealed a hemoglobin of 12.4 gm., a red-cell count of 4,200,000 and a white-cell count of 8900 with 75 per cent neutrophils. Urinalysis revealed a specific gravity of 1.010, + albumin and a rare leukocyte. The blood nonprotein nitrogen was 42 mg. per 100 cc. The fasting blood sugar was 82 mg. per 100 cc. Prothrombin times, Tromexan doses and a record of hemorrhage are recorded in Figure 2.

On the next morning (March 17) calf tenderness was striking, with cord-like tender areas between the heads of the left gastrocnemius. A diagnosis of acute thrombophlebitis was made, and treatment with Heparin and Tromexan was begun. Heparin was discontinued on March 18 at 3:30 p.m. It probably played no part in the hemorrhage that followed approximately 40 hours later on March 20.

On March 19 the patient had improved slightly but was still complaining of abdominal distention and pain. He was coughing a slight amount of blood-streaked mucus.

On the following day, the patient was worse. The apex impulse was found in the 7th intercostal space at the anterior axillary line. The liver was 7 cm. below the xiphoid process and was tender. A pronounced gallop rhythm was present. The lungs were filled with coarse, bubbling rales. Percussion was impaired over the right lower lobe posteriorly. It was thought that a pulmonary infarct had developed in that lobe.

All day the patient coughed bright-red blood. However, this fact did not come to the attention of the staff until 7:30 p.m., when the intern noted a kidney basin full of blood by the bed. Anticoagulants were stopped at once. A whole-blood transfusion of 250 cc. was given at 11 p.m., together

with Hykinone, 72 mg. intravenously, every 3 hours for 6 doses.

By the next morning the hemorrhage was less intense, but the patient was still coughing blood. His blood pressure was 128/74. His color was pale, the pulse was regular at 100 and the respirations were 18. The chest was full of sticky moist rales.

The hemoglobin, which had been 12.4 gm. on admission, dropped to 10.6 gm. on March 22 after the hemorrhage.

The hemorrhage gradually stopped, and the patient improved slowly. By March 27 the hemoglobin had risen to 12.6 gm. The only other complication noted during this period revealed a prominent pulmonary artery and an enlarged left auricle.

An electrocardiogram showed a ventricular rate of 68, auricular fibrillation and a QRS complex of 0.08 second. Depressed ST segments and diphasic T waves were noted in leads V_2 through V_6.

Examination of the blood revealed a hemoglobin of 14.9 gm., 5,040,000 red cells and a white-cell count of 12,100, with 72 per cent neutrophils, 24 per cent lymphocytes, 1 per cent eosinophils and 2 per cent monocytes. Examination of the urine revealed a specific gravity of 1.018, a trace of albumin, no sugar, occasional leukocytes and 6 to 8 erythrocytes per

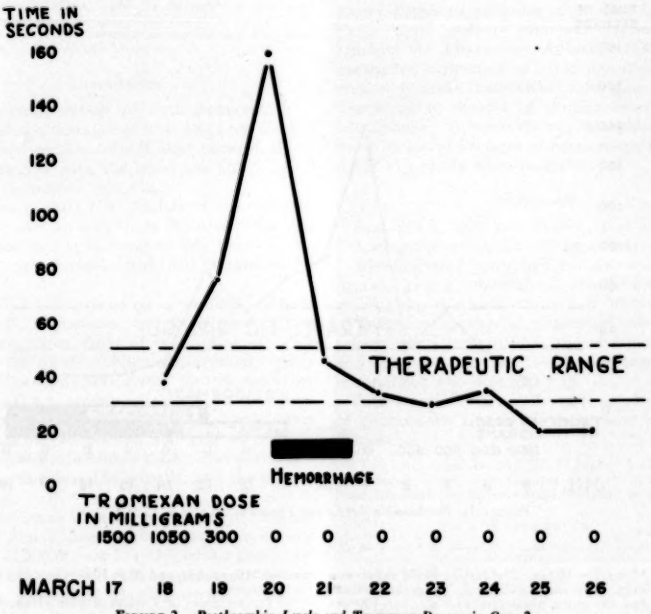

FIGURE 2. *Prothrombin Levels and Tromexan Dosage in Case 2.*

of hospitalization was a temporary right hemiplegia on March 26, probably due to a cerebral angiospasm. There was quick response to a stellate block with procaine hydrochloride. On April 4, 1950, the patient was discharged, free of congestive heart failure. He was last seen in May, 1951, and was doing well.

CASE 3. D. T., a 44-year-old man, entered the hospital on April 21, 1950, complaining of shortness of breath and cough of four months' duration. Positive physical findings included a totally irregular cardiac rhythm, with an apical rate of 80. The mitral first sound was prominent and snapping. A distant diastolic murmur, variously described as blowing or rumbling, was heard best in the left lateral position at the apex. The pulmonic second sound was not accentuated. Along the left sternal border a diastolic murmur of blowing character was audible. The lungs were clear. The liver and spleen were not felt. No peripheral edema was found. Venous pressure and circulation times were normal. Fluoroscopy high-power field. The basal metabolic rate was −6 per cent. The blood nonprotein nitrogen was 32 mg. per 100 cc. A chest x-ray film showed a clear parenchyma and an enlarged heart.

A diagnosis of rheumatic heart disease, Class III, with mitral stenosis and insufficiency and aortic insufficiency was made. He was released on April 27, on a 1-gm. salt diet, digitalis and ammonium chloride.

That evening at home the patient had a sudden episode of nausea, vomiting and right-flank pain. This subsided in 45 minutes. On May 11 he was seen in the Out Patient Clinic; he was feeling better but was not working.

At 1 p.m. on June 22 he developed pain in the right lower quadrant and right flank; he had passed three watery stools before a physician saw him at 3:45 p.m. At that time it was thought that he had an exacerbation of his functional bowel distress but consideration should be given to the possibility of a mesenteric embolus. He was admitted to the hospital under the care of the Gastro-Intestinal Division.

Examination on admission showed an anxious man who appeared acutely ill. The blood pressure was 135/70. Auricular fibrillation was present. The abdomen was soft and showed a slightly increased resistance in the right lower quadrant. The liver, spleen and kidneys were not palpable. There was no rebound tenderness.

Examination of the blood disclosed a hemoglobin of 15.3 gm., a red-cell count of 4,700,000 and a white-cell count of 19,600, with 86 per cent neutrophils, 11 per cent lymphocytes and 3 per cent monocytes. Examination of the urine revealed a specific gravity of 1.022, ++++ albumin, + sugar, +++ erythrocytes and occasional leukocytes. The blood nonprotein nitrogen was 37 mg. per 100 cc. The fasting blood sugar was 103 mg. per 100 cc. Diastase was 40 units. The serum sodium was 306 mg. and the serum potassium 13.8 mg. per 100 cc. The whole-blood chlorides were 618 mg. per 100 cc.

The lack of positive findings, coupled with great anxiety on the part of the patient, made it difficult to establish a diagnosis. Under conservative management the pain subsided. Barium-enema examination and retrograde pyelograms were negative.

At 10:30 a.m. on July 5, the patient suddenly collapsed while talking with another patient. Examination revealed extreme restlessness and inability to speak. The right pupil was dilated, although both pupils reacted to light. There was paralysis of the right facial muscles, the right arm and the right leg. Deep tendon reflexes were decreased on the right, and a right-sided Babinski reflex was present. Lumbar puncture revealed a water-clear fluid.

A diagnosis of cerebral embolus was made, and the patient was transferred to the Cardio-Respiratory Division. A stellate ganglion block was done, and a Horner syndrome was produced with no improvement. The patient was placed in an oxygen tent. Anticoagulants were begun. Heparin was given intravenously, 75 mg. every 4 hours, if required, beginning at 1:15 p.m. on July 5. The dose was given according to the Lee-White clotting time. The first dose of Tromexan was given at 3:30 p.m.

The last dose of Heparin was given at 7 a.m. on July 6. It was not until July 9, 72 hours later, that the prothrombin time exceeded the therapeutic range and hematuria developed. The effect of Heparin given intravenously may be presumed to have subsided long before.

Figure 3 correlates the prothrombin times and amount of Tromexan given with the hemorrhage that followed.

By July 8 the patient had improved enough to be taken out of the oxygen tent, but the flaccid paralysis and aphasia continued. Microscopic hematuria continued, suggesting the possibility of a renal infarct. On July 9 the prothrombin time

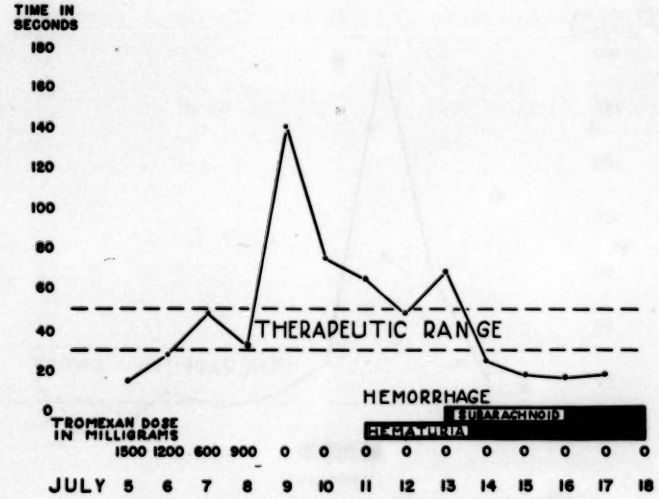

FIGURE 3. *Prothrombin Levels and Tromexan Dosage in Case 3.*

reached 140 seconds, and 20 to 30 erythrocytes per high-power field were seen.

No further doses of Tromexan were given. On the following day the prothrombin time had dropped to 75 seconds, but microscopical examination showed the urine to be packed with erythrocytes. Since the prothrombin curve was falling, it was decided to continue conservative therapy — that is, withholding of Tromexan and keeping whole blood and vitamin K available. The urine became grossly bloody on July 11. By July 12 the prothrombin time was down to 48 seconds, and conservative management was continued.

On July 13 the prothrombin time rose to 69 seconds, indicating severe derangement of the clotting mechanism, as no anticoagulant had been given for five days. Physical examination that day disclosed nuchal rigidity, and it was believed that a subarachnoid hemorrhage had occurred. In view of the new hemorrhage, Synkavite, a water-soluble vitamin K preparation, was given intravenously at 9 p.m. in a dose of 72 mg. This dose was repeated twice on July 14, at 3 a.m. and 9 a.m. — a total of 216 mg.

The urine was free of gross blood on July 14, but the stiff neck persisted, and the patient remained unresponsive. The prothrombin time dropped rapidly toward normal after the vitamin K therapy, but the patient's condition slowly deteriorated. His fever began to rise, Cheyne–Stokes respira-

tions developed and he became comatose. He died at 1:06 a.m. on July 18.

Autopsy revealed a dilated heart with a greatly thickened and stenotic mitral valve. The orifice was less than 1 cm. wide when open. No thrombi were found in the heart. A few small subendocardial petechial hemorrhages were seen. The lungs showed minimal chronic passive congestion. The left kidney showed two healed infarcts. In the right kidney evidence of considerable fresh hemorrhage was noted. When the dura mater was opened blood was found in the subarachnoid space, and fresh blood was seen over the lateral and posterior hemisphere and over the base of the brain. No aneurysm or other lesion could be found as a source of the bleeding.

After fixation the brain revealed a thin film of hemorrhage within the subarachnoid space extending over the convexity of the parietal lobe and the inferior and medial part of the left occipital lobe. On the right the hemorrhage was more extensive, occupying all the space over the right parietal lobe and occipital lobe. It also covered the cerebellum. The blood vessels showed no appreciable lesions.

Discussion

In the administration of anticoagulants, it is considered that a therapeutic level has been reached when the prothrombin time is kept between thirty and fifty seconds with the one-stage Quick test,[11] made with undiluted plasma.

Wright states that the ideal level lies between two and two and one-half times the control for that day, provided that it is under twenty seconds. He states that this formula was first suggested by Nichol.[5]

Figure 2 shows the prothrombin time of 75 seconds on March 19. Tromexan had been used in our clinic for only three weeks at that time. We were aware that the prothrombin time returned rapidly to normal if no drug was given. Furthermore, we considered 300 mg. a minuscule dose. In consideration of a pulmonary infarction and a continuing threat of thromboembolism, 300 mg. was given, despite the low prothrombin time. The next day's prothrombin time was 158 seconds, and the patient was bleeding.

The difficulties in Case 1 arose primarily from the attempt to find a daily maintenance dose. Note that a dose of 300 mg. on May 17, with a prothrombin time of fifty-two seconds, caused a rise of only five seconds, whereas on May 21, with a prothrombin time of forty-nine seconds, the same dose caused a rise of three hundred and eleven seconds. One factor that affects this comparison is that on May 17 the prothrombin curve was falling, whereas on May 21 it was rising. This indicates that consideration of the prothrombin time of the current day alone is not sufficient basis on which to determine dosage. The general trend of the prothrombin curve must also be considered. Additional anticoagulant is needed in the presence of a falling curve to maintain a therapeutic level, and less is required when a rising curve is present. Case 2 likewise illustrates this point.

Case 3 also exhibited a severe reaction to what was considered a therapeutic dose of Tromexan.

These patients had several characteristics in common. They were extremely ill. Their clotting mechanisms were easily deranged. Once deranged, coagulation did not return to normal for several days, even though blood transfusions and vitamin K were given. Yet none of the patients had had previous hemorrhagic tendencies, and each case presented a clear indication for anticoagulant therapy.

In conclusion, it seems apparent that the use of Tromexan is not without hazard. There seems to be no diagnostic criterion that will indicate in advance those patients who may become suddenly sensitive to Tromexan. Although the previously mentioned properties of rapid absorption and excretion do make it somewhat safer than Dicumarol, Tromexan is capable of causing serious or fatal hemorrhage. It behooves anyone using Tromexan to be on guard for signs of hemorrhage and to combat it vigorously when indicated.

Summary

One death and two nearly fatal hemorrhages following the use of Tromexan are reported.

Bleeding was controlled by discontinuing Tromexan, giving whole-blood transfusions and administering synthetic vitamin K intravenously.

Tromexan appears to possess an extra margin of safety over Dicumarol because of rapid absorption and excretion but can cause hemorrhage, especially in a patient who is seriously ill.

Safe use of Tromexan depends on the observance of precautions similar to those now in use with Dicumarol.

The author is indebted to Dr. F. Janney Smith, physician-in-charge of the Cardio-Respiratory Division of the Henry Ford Hospital, for his encouragement and helpful criticism.

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PROLONGED CATION-EXCHANGE RESIN THERAPY IN CONGESTIVE HEART FAILURE*

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IN THE past few years increasing clinical interest has been manifested in the ion-exchange resins. These are of two principal types, anion and cation. Anion-exchange resins have been used as antacids and pepsin inhibitors in the management of patients with peptic ulcer.[1-6] Cation-exchange resins are of two common types: sulfonated and carboxylated. Either of these may be saturated with ammonium, hydrogen, potassium or other cations. Their value in the management of congestive heart failure and other related disorders associated with sodium-ion retention and edema is emerging gradually through clinical experience.[7-14] Dock[8] in 1946 first suggested that cation-exchange resins might be used for the removal of sodium from the body. Initial observations were made on animals with regard to toxicity and fecal sodium content. Irwin,[11] in 1949, using an ammonium-saturated sulfonated cation-exchange resin, demonstrated by balance studies its effect on serum, urine and fecal sodium, potassium and calcium. It was noted that potassium was lost in the stool, by the same mechanism as sodium was lost, in amounts sufficient to cause significant lowering of the serum potassium and potential clinical hypokalemia. Loss of calcium was not found to be great but was considered a potential danger. Hay and Wood[13] recently reported the use of short courses of both the ammonium and ammonium-potassium forms of carboxylated resin in several patients with edema of varied origin. No serious toxic effects were noted, although hypokalemia was encountered in the use of the ammonium form of resin. Mercurial diuresis was found to be potentiated, and favorable results in mobilizing edema fluid were obtained in 6 of 8 patients. No data are available at present concerning the efficacy and possible deleterious effects of prolonged therapy with cation-exchange resins. The purpose of this paper is to offer a preliminary report on the long-term continuous use of a cation-exchange resin in patients with chronic congestive heart failure, with principal reference to its therapeutic value and toxicity.

Resodec,§ the exchange resin used in the patients described in this report, is an acrylic polymer of heavy molecular weight, whose carboxylic radicals can readily adsorb and release cations to which they are exposed. The resin is initially saturated with both ammonium and potassium ions, in a ratio of about 3 to 1. In the stomach, these cations are exchanged for hydrogen ions. In the bowel, in which the pH is suffciently high for their release, the hydrogen ions are exchanged for sodium and potassium and, to a lesser extent, other cations. Sufficient potassium is supplied with the resin to replace that which is adsorbed on the resin and lost in the stool.

Three ambulatory patients were selected for study because they exhibited long-standing chronic cardiac decompensation uncontrolled by the usual effective therapeutic measures, including rest, rigid dietary sodium restriction, digitalization and mercurial diuresis. Recurrences of severe heart failure had necessitated several hospitalization periods in each case. These patients were given cation-exchange resin daily for periods of five to nine months.

Before resin therapy was initiated each patient was stabilized on a regimen of rest, digitalis, regularly administered mercurial diuretics and a strict diet containing 500 mg. (22 milliequiv.) of sodium, 1270 mg. (36 milliequiv.) of chloride and 40 gm. of protein. Detailed dietary instructions were given by a special dietitian, who interviewed patients on each subsequent visit, paying particular attention to diet palatability, calculated weekly sodium intake and voluntary and involuntary dietary infractions. Control determinations of the serum concentrations of calcium, potassium, sodium, chloride, carbon-dioxide combining power and nonprotein nitrogen and of twenty-four-hour urine sodium and chloride were made. Patients were instructed to take the finely powdered resin in doses of 15 gm. three times daily with meals. The resin was usually mixed with fruit juice or milk or with food, such as mashed potatoes or apple sauce. Added calcium was given as calcium lactate, 5 gm. daily, or as milk, 16 ounces daily. Supplemental vitamins were also given. Patients were followed at weekly or biweekly intervals, with particular attention devoted to drug side-effects, weight, edema, moisture in the lungs, blood pressure and exercise tolerance. On each return visit determinations of the serum calcium, potassium, chloride and carbon-dioxide combining power and of the twenty-four-hour urinary excretion of sodium and chloride were made. Blood nonprotein nitrogen, hematocrit and hemoglobin values were determined at monthly intervals.

CASE REPORTS

CASE 1. D. B., a 57-year-old man, has hypertensive and coronary heart disease, marked cardiac enlargement, chronic congestive heart failure and nephrosclerosis with mild renal insufficiency. He has been followed in the Duke Hospital out-patient department since 1937, at which time his blood

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§The resin used in this study was supplied for experimental purposes by Smith, Kline & French Laboratories of Philadelphia, Pennsylvania.

pressure was recorded as 210/150. Congestive heart failure was first noted in 1947. At that time he was placed on digitalis and a rigid low-sodium, low-protein diet. During the subsequent 3 years there was fluctuation between borderline and frank congestive failure; mercurial diuretics were required as often as twice weekly. In February, 1950, he was hospitalized for 3 weeks because of heart failure. The basic rice diet[15] was afterwards employed with temporary improvement, but the patient was not able to adhere to this more rigid regimen and consequently decompensation redeveloped in May, 1950, requiring mercurial diuretics 2 to 3 times weekly. He then returned to a 500-mg.-sodium, 40-gm.-protein diet; 4 weeks later he was started on the cation-exchange resin, 45 gm. per day. An immediate drop in weight followed, and in spite of frequent dietary infractions his weight remained stable until August, 1950, when two 2-cc. injections of mercuhydrin were required. In September, after 12 weeks of base-line studies, an additional 500 mg. (22 milliequiv.) of sodium was given daily, as dissolved tablets of sodium chloride to be sprinkled on his food. The daily allotment of added sodium was increased monthly thereafter in an attempt to determine the patient's tolerance to salt while he was taking resin. By late November, 1950, he was taking a calculated total of 2300 mg. (100 milliequiv.) of sodium daily, with resultant gradual weight gain, edema formation and decrease in exercise tolerance. He was maintained on this relatively high sodium intake for 9 weeks. Weekly injections of mercury were necessary after the fifth week because of increasing edema. On January 19, 1951, the sodium intake was reduced to 1380 mg. (60 milliequiv.). Mercurial diuretics have been required only once in 10 weeks on this sodium intake.

Comment. This patient with chronic intermittent congestive heart failure had been treated for three

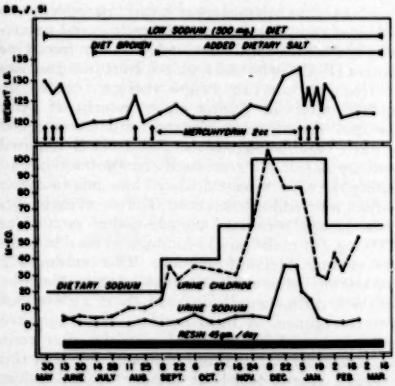

FIGURE 1. *Laboratory Findings on Patient D. B.*

years by conventional means without success. He was unable to adhere to a regimen of sodium restriction of a degree sufficient to prevent decompensation. On resin therapy in conjunction with a 500-mg.-sodium diet, in spite of occasional dietary infractions and calculated addition of dietary sodium, he remained free of heart failure and was capable of greatly increased activity for nine months. Mercurial diuretics were needed only after the addition of 1840 mg. (80 milliequiv.) of sodium to his diet. Since he has required no additional mercury after stabilization on an intake of 1380 mg. (60 milliequiv.) of sodium daily, this amount probably represents the maximal allotment of sodium permitted by resin therapy for this patient.

CASE 2. P. C., a 67-year-old man, has hypertensive heart disease, probable rheumatic heart disease with cardiac enlargement, auricular fibrillation and mild renal insufficiency. He has been followed in the Duke Hospital out-patient clinic since 1945, at which time congestive heart failure was

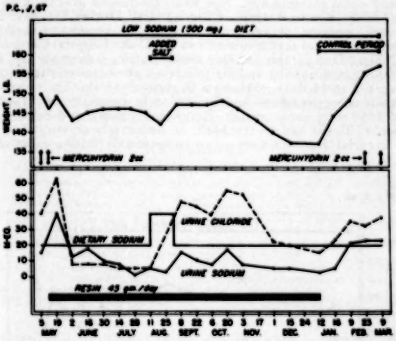

FIGURE 2. *Laboratory Findings on Patient P. C.*

first diagnosed. This was managed by digitalis and rest with fair compensation until January, 1948, when he was admitted to Duke Hospital with frank congestive failure of 3 weeks' duration. He improved when placed on a strict 500-mg.-sodium diet in addition to digitalis but required occasional injections of mercurial diuretics. Despite what was considered adherence to the prescribed regimen, he was readmitted with frank congestive failure in December, 1949. During the month after his discharge from the hospital he gained 22 pounds and for the next 4 months required frequent administration of mercurial diuretics and strict limitation of activity. In May, 1950, he was started on continuous resin therapy, 45 gm. daily, in addition to the low-sodium diet and digitalis. During the following 8 months he remained free of failure, increased his activity level markedly, had no weight fluctuation or edema and required no mercurial or other diuretics. During three weeks in August, 1950, 500 mg. (22 milliequiv.) of additional sodium was allowed, but this was discontinued because of anxiety on the part of the patient. On January 12, 1951, after 8 months of continuous administration, the resin was discontinued for a control period on diet and digitalis alone. In the subsequent 8 weeks he gained 20 pounds, became much more dyspneic on exertion and developed ++ pitting ankle edema, engorged neck veins and moist rales at the lung bases. These signs and symptoms subsided rapidly when resin therapy was resumed.

Comment. This patient had been treated for intermittent congestive heart failure for five years, with decreasing success during the last two years. Hospitalization, frequent use of mercurial diuretics and marked restriction of activity were required. During eight months of resin therapy, with continuation of rigid dietary sodium restriction, he remained free of failure and increased his activity level markedly. When resin therapy was discon-

tinued, heart failure recurred within eight weeks. In the sixth month of resin therapy this patient experienced an episode of upper-gastrointestinal bleeding, for which no site could be demonstrated by x-ray. He had had one previous similar episode in 1945. It is thought that this complication was coincidental and probably not related to resin therapy.

CASE 3. M. C., a 46-year-old woman, has rheumatic heart disease with mitral stenosis, mitral insufficiency, auricular fibrillation, a history of chronic congestive heart failure and mild renal insufficiency. She had experienced gradually increasing exertional dyspnea for 6 years. During the past 3 years, because of recurrent episodes of congestive heart failure, she was seen frequently in the Duke Hospital Cardiac Clinic. During this period, despite strict adherence to a 500-mg.-sodium diet and digitalization, she required diuretics every 7 to 14 days. Attempts to restore the rhythm to normal during periods of hospitalization in February and June of 1950 were unsuccessful. Between February and September, 1950, she had several bouts of moderately severe failure. Mercurial diuretics were given twice weekly during most of

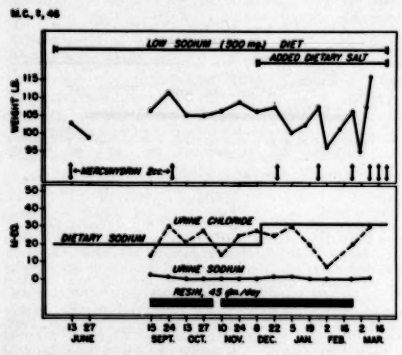

FIGURE 3. *Laboratory Findings on Patient M. C.*

this period. In September, 1950, resin therapy was begun, — 45 gm. per day, — as a supplement to the 500-mg.-sodium diet and digitalis. During 3 months of this regimen, mercurial diuretics were needed only once. Her weight remained constant, and she remained free of failure. There was moderate improvement in her exercise tolerance. For the next three months 500 mg. (22 milliequiv.) of added sodium in the form of dissolved tablets of sodium chloride was allowed. Mercurial diuretics were given on three occasions during this interval because of gradual weight gain and decreased exercise tolerance. On February 23, 1951, resin was discontinued for a control period on the 500-mg.-sodium diet with 500 mg. (22 milliequiv.) of added sodium. During the following 14 days the patient gained twenty pounds and exhibited pitting ankle edema, moist rales at the lung bases and a definite increase in exertional dyspnea.

Comment. This patient experienced increasingly severe episodes of congestive heart failure over a six-year period. Despite comparatively rigid sodium restriction, digitalization and the frequent use of mercurial diuretics, she grew progressively worse. During a three-month period of continuous resin therapy and a 500-mg. sodium diet only one injection of mercury was required. When resin therapy was discontinued, congestive failure rapidly returned.

DISCUSSION

Patients with congestive heart failure tend to accumulate excess fluid as a result of the inability of the kidney to rid the body of excess sodium ions. There is a direct relation between the degree of sodium-ion retention and the degree of edema formation and other signs and symptoms of congestive failure. The practice of restricting dietary sodium is well accepted as a means of preventing and remedying excess fluid accumulation. However, diets containing 500 mg. of sodium or less per day are often difficult to follow because of their unpalatability and monotony. Moreover, low-sodium diets of this type, even when strictly adhered to, may not be sufficiently restrictive to prevent heart failure. This is exemplified by at least two of the three cases reported here. Through the use of a cation-exchange resin, a virtually inert and completely nonabsorbable substance capable of removing sodium ions from the bowel, in conjunction with a 500-mg.-sodium diet and digitalis, three patients who had been managed with great difficulty over periods of several months on the same low-sodium diet and digitalis became relatively free of failure. Each patient's exercise tolerance was greatly improved; two remained completely free of dependent and pulmonary edema; the third remained relatively free. One patient (P. C.), who had required mercurial diuretics at frequent intervals before therapy, needed no further injections during eight months of resin therapy. Shortly after the resin was discontinued he again required mercurials. Patient D. B. required mercury only after a severe dietary infraction and during the time when calculated amounts of excess sodium were added to his diet. The use of exchange-resin therapy permitted the addition of as much as 1000 mg. (44 milliequiv.) of sodium to his diet without causing edema formation. This produced a marked improvement in his morale and enabled him for the first time to adhere faithfully to a prescribed dietary regimen. A third patient, M. C., required only occasional injections of mercury after resin was administered. It is of interest to note that this patient's twenty-four-hour urinary sodium values remained consistently below 1 milliequiv. during resin therapy and at times were as low as 4 mg. per twenty-four hours. Two of the three patients excreted as little sodium* in twenty-four hours as does the average patient who adheres strictly to the basic rice-diet regimen.[16] It was noted that twenty-four-hour urine-chloride values closely paralleled the actual dietary intake of sodium in milliequivalents. This served as a useful guide in de-

*The average urinary sodium excretion on the basic rice diet is, according to Kempner, 11 mg. (0.5 milliequiv.) per twenty-four hours. Patient D. B. excreted an average of 20 mg. (0.87 milliequiv.) and patient M. C. an average of 12 mg. (0.51 milliequiv.) per twenty-four hours while on a 500-mg. (22 milliequiv.) sodium diet and resin therapy.

tecting voluntary and involuntary dietary infractions. Patient P.C., whose urinary chloride output fluctuated widely at times, intermittently used a salt substitute containing potassium chloride.

In spite of severe sodium depletion resulting from dietary restriction with continuous long-term resin therapy, the low-sodium syndrome was not encountered in these patients. Serum sodium values remained in the low-to-normal range, as did the values for serum calcium and carbon-dioxide combining power. Despite mild renal insufficiency in these patients, no clinical or laboratory evidence of hypokalemia or hyperkalemia was found. The blood pressure of the two hypertensive patients was lower during the period of resin therapy than previously. Such complications as azotemia, clinical acidosis and hemoconcentration were carefully watched for but were not observed. One patient, M.C., noted severe constipation while taking resin. This was finally alleviated by the use of laxatives and an increase in fluid intake. Patients occasionally complained of the taste of resin but in general had no difficulty in ingesting it in fruit juice or milk or mixed with food.

Summary and Conclusions

Three patients suffering from long-standing congestive heart failure who had responded poorly to conventional methods of treatment, including rigid dietary sodium restriction, have been studied during the continuous administration of cation-exchange resin for periods of five to nine months.

Each patient showed definite improvement while taking resin, as evidenced by stability of weight, failure to develop edema, improved exercise tolerance and lowered requirement of mercurial diuretics.

Frequent determinations of serum and urine electrolytes were made. Extremely low twenty-four-hour urinary sodium-excretion levels were noted. No serious serum-electrolyte disturbances were observed.

No unfavorable signs or symptoms were encountered despite the concomitant continuous use of relatively strict low-sodium diets and resin for periods varying from five to nine months. However, it should be emphasized that such patients must be followed carefully, particularly with regard to potential azotemia, acidosis, hypocalcemia, hypokalemia, hyperkalemia and the low-sodium syndrome.

It is concluded that the prolonged continuous or intermittent use of a cation-exchange resin is a useful adjunct to the present treatment of congestive heart failure. Indeed, it is believed that compensation would not have been possible in the cases herein reported without the use of a cation-exchange resin.

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MEDICAL PROGRESS

ELECTROLYTE AND FLUID DISTURBANCES IN CONGESTIVE HEART FAILURE*

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HEART failure primarily denotes failure of the heart as a pump — a deficiency in its ability to maintain an adequate blood flow to the tissues according to their needs under a physiologic range of requirements. Concomitantly, there is impairment of the capacity of one or more of the cardiac chambers to accept and expel the venous return. In consequence there are disturbances in flow and pressure and secondary physical and metabolic disturbances in various tissues.

From the point of view of the clinician, heart failure is defined differently — as a syndrome characterized by breathlessness, orthopnea, nocturnal dyspnea, cardiac asthma, pulmonary edema, enlargement of the liver, engorgement of superficial veins and, eventually and most characteristically, edema, ascites and hydrothorax. Most of these manifestations may be explained by disturbance in distribution or by retention of water in the body, excessive in degree and abnormal in localization. Furthermore, their amelioration or disappearance is associated with and dependent on the elimination and redistribution of this excessive fluid.

The purpose of this discussion is to present the aberrations in water and electrolyte content and distribution found in congestive heart failure and to consider some possible steps between the deficient cardiac output, which is probably a primary physiologic disturbance in heart failure, and these secondary electrolyte and water abnormalities. We will start with a consideration of the body water in regard to its quantity and distribution and their control and the manner and mechanism of its alteration in congestive heart failure. This discussion is designed to raise questions and to point up the inadequacies of present knowledge in this regard, rather than to present a neatly catalogued and completed body of knowledge.

BODY WATER AND BODY-WATER COMPARTMENTS

Although body water diffuses freely through the various cellular and vascular membranes, it may be regarded as more or less quantitatively segregated into various compartments, the intracellular and the extracellular, the latter being subdivided into the vascular and interstitial compartments. The relative integrity of these compartments is maintained by the membranes of the cells and of the blood vessels — the vascular membrane by virtue of its relative impermeability to serum proteins and the cell membranes by similar impermeability to cell protein and by their selective permeability to various electrolytes.

Measurement of the total body water and of the quantity within the various compartments is beset with technical difficulties; often there is uncertainty concerning the validity of the results obtained. Nevertheless, useful data have been provided by the available methods. In general, a substance is injected that diffuses evenly and rapidly throughout the blood stream (to determine plasma volume) or throughout the entire extracellular space (to determine extracellular volume) or throughout the extracellular and intracellular space (to determine total body water). When equilibrium, that is, uniform mixing, is obtained, a sample of blood is withdrawn and the concentration of the injected sample determined. The volume of the fluid throughout which the injected substance was diffused is equal to the quantity of the substance injected divided by its concentration in this fluid after equilibrium. This assumes that the injected substance remained exclusively within the compartment measured, was not excreted from the body during the test period and was not increased or diminished in amount by metabolic processes or storage. If the substance is excreted or metabolized or enters other compartments, it must be possible to correct accurately for this loss. In addition, the injected substance must be nontoxic, rapidly diffusible and without influence on body hydration. It should be relatively easy and inexpensive to use and to measure analytically.

The dye Evans blue (T–1824) is commonly employed to measure the plasma volume.[1] Albumin or plasma containing radioactive iodine may also be used for the same purpose.[2] Radioactive iron[3,4] or phosphorus[5] has served to measure the erythrocyte volume from which the plasma volume is calculated by determination of the hematocrit. The latter introduces an error, as the venous-blood hematocrit is not an accurate average of the total blood hematocrit.

Potassium thiocyanate[6,7] has been commonly injected to determine the extracellular fluid volume, but bromide[8,9] and radioactive sodium[10] have also been used, among other substances. More recently inulin[11,12,30] and ferrocyanide[13] have been regarded as yielding more accurate measurements of the extracellular volume. Because there is considerable uncertainty concerning whether the space into which these substances diffuse actually represents the extracellular volume, it is preferable to

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express the values obtained as the "volume of distribution"[14] of thiocyanate, of radioactive sodium or of inulin or as the thiocyanate "space" or the inulin "space."

The total body water has been measured by the oral administration or intravenous injection[15, 16] of a known quantity of deuterium oxide (heavy water) and by tritium oxide.[17] These involve difficult and expensive procedures. Recently antipyrine[18] and N-acetyl 4-amino-antipyrine[19] have been used; the measurements obtained approximated those determined by deuterium oxide and those calculated from the specific gravity of the body.[20-22]

The interstitial fluid volume (extravascular extracellular fluid) is calculated by subtraction of the plasma volume from the extracellular volume; the intracellular volume is calculated by subtracting the extracellular volume from the total body water.

It is doubtful whether any of the substances used to determine plasma or extracellular or total body water satisfy the idealized requirements mentioned above. Furthermore, the technical difficulties and inaccuracies in our methods increase substantially when we try to measure these components of body water in cases of congestive heart failure. The accumulation of extracellular fluid impairs both the speed of diffusion and the uniformity of mixing, and this deficiency is enhanced in the presence of effusions in the serous cavities. For these reasons the figures cited as representing body water and its components in health and in heart failure must be regarded as tentative approximations.

With due regard for these shortcomings, the following table offers the approximate values of body-water components in the normal person and in congestive heart failure (Table 1).

The first column shows in average figures the size of the various compartments of body water expressed as percentages of body weight. The total body water forms about 56 per cent of the body weight, according to studies with heavy water and antipyrine.[18, 23] This figure is lower than the 70 per cent formerly regarded as representing body water on the basis of desiccation studies in the dog[24] and human beings.[25] Variations in body fat considerably modify the percentage of body weight due to water. If body water is considered in relation to fat-free or lean body mass, it is more constant and averages about 72 per cent.[26, 27]

The extracellular water, formerly represented as forming 20 to 30 per cent of body weight,[9, 10, 15, 28-30] according to determinations with thiocyanate, bromide or radioactive sodium (Na^{24}) is now regarded as being fairly constant at 16 per cent of body weight, according to the inulin method.[20-22] The higher figures previously obtained are believed to be due to the entrance into certain cells of thiocyanate, sodium and the other test substances used. The intracellular fluid volume is represented as approximately 40 per cent of body weight by subtraction. The plasma volume is actually somewhat less than the 5 per cent represented in the table.[1]

The second column shows figures (in liters) for the various components of body fluid in a normal person weighing 60 kg. and having a surface area of 1.7 sq. meters.

In the last column, by contrast, are the corresponding values when such a patient has gained 12 kg. solely because of fluid retention in heart failure. The total body water is 12 liters more than normal — that is, 45 instead of 33 liters.[22] When there are large and rapid changes in total body water, as in the accumulation or loss of edema fluid in heart failure, there is no need for repeated determinations of body water. Such changes in body water may be estimated with sufficient accuracy by careful serial measurements of body weight. The plasma volume in this patient with congestive heart failure increased approximately 45 per cent, or 1.2 liters.[31, 32] Relatively few determinations of inulin space have been made in patients with congestive heart failure, and no such determination was actually made in the patient under consideration. However, with the degree of edema represented in this case, other studies have indicated that the inulin space is usually more than doubled.[20] In this instance we are therefore postulating an extracellular space of 33 per cent instead of the normal 16 per cent. Thirty-three per cent of 72 kg. is 24 liters. Accordingly, the interstitial fluid would amount to 20.2 liters instead of the normal of 7 liters. It is apparent that in the edematous cardiac patient the extravascular portion of the extracellular fluid, that is, the interstitial space, contains most of the retained fluid, whereas the plasma volume is relatively moderately increased. The calculations in this example suggest likewise that there is some, — but slight, — intracellular dehydration. The possibility of the development of extracellular overhydration with intracellular dehydration is supported by clinical observations in edematous cardiac patients.

Despite the free diffusibility of water, the water retained in congestive heart failure is not divided proportionally into the various fluid compartments; the excess is almost all in the interstitial fluid. It

TABLE 1. *Distribution of Body Water in Normal Persons and in Congestive Heart Failure.*

COMPARTMENT	IN NORMAL PERSONS		IN HEART FAILURE	
	PERCENTAGE OF BODY WEIGHT	LITERS (WEIGHT 60 KG.)	PERCENTAGE OF BODY WEIGHT	LITERS (WEIGHT 72 KG.)
Plasma	5	2.6	5	3.8
Interstitial	11	7.0	28	20.2
Extracellular	16	9.6	33	24.0
Intracellular	40	23.4	30	21.0
Total body water	56	33.0	63	45.0

is the quantity of fluid in this compartment that determines the presence of edema. Note that the increase in quantity of interstitial fluid far exceeds the total of plasma volume. There is a much greater tendency to maintain the constancy of the plasma volume than to maintain the constancy of the extravascular portion of the extracellular fluid. Massive infusions of saline solution in normal animals may more than double the volume of the extracellular fluid, whereas that of the plasma is virtually unchanged.[35] It would be desirable to have more accurate values for the compartmental distribution of water in heart failure for a better understanding of the mechanisms involved in fluid-electrolyte disturbances and as a basis for improving therapy.

Classification of Disturbances in Electrolytes and Body Water

A discussion of body water is intimately bound with a consideration of its concentration of electrolytes. The living cell is dependent on a fairly constant osmotic pressure and a similarly constant hydrogen-ion concentration of the body fluids in which it is bathed; these in turn depend on the constancy of electrolyte concentrations. Homeostasis in these respects is usually attained by mechanisms that closely correlate the quantity and distribution of body water and the concentration of electrolytes. When the quantity of body water is increased or diminished there is a corresponding quantitative increase or reduction in electrolytes and the *concentration* of electrolytes remains constant. When there is a change in the quantity of one without a corresponding change in the other, the concentration of electrolytes is altered. This modifies the osmotic pressure or the pH of the body fluids or both. Rigid homeostasis is an ideal — not always attainable under physiologic stress, especially the stress of disease, such as in heart failure.

Table 2. *Disturbances in Sodium-Water Balance.*

	Extracellular Fluid Volume	Electrolyte Concentration
Sodium retention	++	= + or −
Sodium depletion	− or +	−
Water deprivation	−	+
Water excess (intoxication)	+	−

+ denotes an increase in quantity of extracellular fluid or hypertonicity of this fluid.
− denotes a reduction in quantity of extracellular fluid or hypotonicity of this fluid.
= denotes normal or unchanged.

Table 2 indicates the varieties of disturbance in electrolyte and water balance. The electrolyte, sodium, is the chief determinant of the osmotic pressure of the extracellular fluid. An increase in sodium concentration is usually followed by retention of fluid, with an increase in extracellular volume and restoration of a normal sodium concentration and a normal osmotic pressure. Similarly, sodium depletion is usually followed by increased water excretion and reduction in extracellular fluid volume, but restoration of normal sodium concentration. Excessive retention or excessive depletion of sodium leads to disturbances in which the electrolyte concentration (and osmotic pressure) as well as the extracellular volume are altered. Similar dissociation of extracellular volume and electrolyte concentration may occur with primary severe dehydration or overhydration.

Increased sodium retention is often characterized by edema; it is observed in heart failure, some forms of nephritis and Cushing's syndrome, after excessive administration of normal saline solution and after excessive doses of desoxycorticosterone and other adrenocortical hormones in the presence of an adequate sodium intake. The extracellular volume is augmented, but in most of these examples the concentration of sodium and other electrolytes in the plasma is normal. In occasional cases of Cushing's syndrome elevation of plasma sodium[36] concentration suggests that there is an increase in osmotic pressure as well as in the volume of extracellular fluid. In congestive heart failure, however, plasma sodium concentration is not infrequently below normal,[37-39] indicating hypotonicity of extracellular fluid when the extracellular volume is greatly expanded.

With *depletion of sodium* and consequent dehydration, the kidneys at first maintain normal sodium concentration and isotonicity of extracellular fluid at the expense of a diminished extracellular volume.[40-42] Later both plasma and extracellular volume are diminished and the sodium concentration is low. Urine concentration is low, azotemia is present and the clinical manifestations of shock may ensue.[43, 44] This may be seen in clinical states in which sodium is lost through the kidney, gastrointestinal tract or sweat, such as Addisonian crises,[45] diabetic acidosis,[46, 47] burns,[48] diarrhea[49, 50] and intestinal fistula.[51] A salt-depletion syndrome has been described in cases of heart failure and occurs occasionally when excessive loss of sodium and chloride results from vigorous and frequent mercurial diuresis at the same time that sodium intake is restricted.[52-55]

Acute water deprivation, with consequent dehydration, may result in a diminished volume of extracellular fluid and may be associated with an increased concentration of sodium and hypertonicity.[42, 56-58] Thirst, dry skin and mucous membranes, scanty concentrated urine and, in severe cases, restlessness and fever are the outstanding features. A similar picture associated with hypertonicity due to increased extracellular sodium concentration may follow excessive urinary losses of water in diabetes insipidus.[59] In cases of heart failure in which water intake was greatly restricted (a common therapeutic recommendation some ten

years ago) mixed forms of water deprivation with sodium-water retention were commonly observed.

Overhydration due to the ingestion of very large quantities of water may rapidly produce the syndrome of *water intoxication*.[80-82] Symptoms may be mild, comprising merely nervousness, restlessness, asthenia, polyuria and pollakiuria, salivation and vomiting. With more intense water intoxication, disorientation, twitching of the extremities, stupor or convulsions may result. A hypertonic solution of sodium chloride usually corrects the condition.[82]

Electrolyte Concentrations of Plasma and Tissues in Health and in Heart Failure

The distribution of body water in normal persons and in patients with congestive heart failure has been discussed. We are concerned now with the corresponding *concentration* of the various electrolytes in the various body water compartments, both in health and in heart failure. The values for normal electrolyte concentration in blood plasma are listed in Table 3. In Table 4 are shown the major electrolyte concentrations in the various body water compartments. Allowing for the very low concentration of nondiffusible protein in interstitial fluid as compared with that in plasma and for the consequent Donnan equilibrium effect, the electrolyte composition of interstitial fluid and that of plasma are very similar.[66] There is a slightly lower concentration of cations, notably sodium, and a slightly higher concentration of anions in interstitial fluid. Serous effusions in congestive heart failure also resemble edema and plasma in their electrolyte concentrations, allowing again for the fact that their protein content is lower than that of plasma but higher than that of edema fluid.

Table 3. *Normal Blood Plasma Electrolytes.*[83]

	mg./100 cc.	milliequiv./liter
Sodium	325	142
Chloride	365	103
Bicarbonate (CO_2)	60 vol./%	27
Potassium	19	4.5
Phosphate	4	2.5
Calcium	11	5.5
Magnesium	3	2.5
Sulfate	1	0.5
Organic acids	20	6.0
Protein	6.5 gm./100 cc.	16.0

In contrast with these values are those for the intracellular electrolytes. There is even less certainty concerning the latter. They are based on tissue analyses[64, 67, 68] and more recently on determinations of tissue biopsy or after injection of radioactive cations.[65, 69, 70] The low concentration of 4 to 5 milliequiv. per liter for potassium in plasma is in noteworthy contrast with its high concentration within the cell. On the other hand, the cell membrane is relatively impermeable to sodium, the dominant electrolyte of extracellular fluid. It was formerly thought that sodium and chloride did not enter cells, except in very small quantities. It now appears probable that the normal concentration of these ions may approximate 30 and 20 milliequiv. per liter respectively. This is suggested by the difference in so-called extracellular space as determined by radioactive Na^{24}, which yields a value of 22+ per cent of body weight, and that of inulin, which gives a value of only 16 per cent. The greater dilution of injected Na^{24}, as compared with inulin, is considered due to penetration of some of the Na^{24} from the extracellular into the intracellular space. Bone and cartilage contain large stores of intracellular sodium, but it is uncertain to what extent it participates in extracellular-intracellular electrolyte exchanges.[70] Studies to determine the concentration of intracellular electrolytes in heart failure are hampered by even greater technical difficulties, but analyses of biopsy specimens of skeletal muscle suggest that there is more sodium and less potassium than normal.[38]

Table 4. *Electrolyte Concentrations.*

	Plasma	Interstitial Fluid	Intracellular Electrolytes[64, 68]
	milliequiv./liter	milliequiv./liter	milliequiv./liter
Na	142	140	14–30 (?)
K	4.5	4.5	115–157 (?)
Cl	101	105	1–20 (?)
HCO_3	27	28	10 (?)

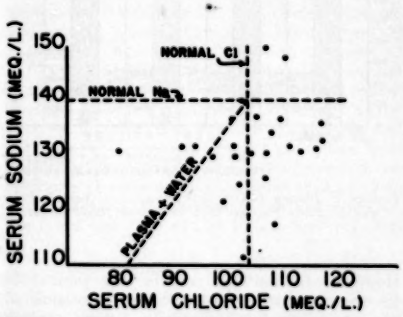

Figure 1. *Serum Electrolyte Concentrations in Congestive Heart Failure.*

Electrolyte Patterns in Heart Failure

Despite the pronounced disturbances in body water content and distribution associated with heart failure, there is usually no striking alteration in the concentration of electrolytes in the extracellular fluid. In view of the known impairment in renal excretion of sodium, one would expect that the consequent sodium retention would tend to

cause an elevation in plasma sodium concentration. On the contrary, in a series of 25 unselected cases of congestive heart failure[37] there was a tendency to a reduction in the concentration of plasma sodium (Fig. 1). These findings of low sodium concentration do not conflict with the basic fact that sodium is retained in the body. Actually, the total amount of sodium in the body is greatly increased because the 100 to 150 per cent increase in extracellular fluid much more than compensates for a 5 to 10 per cent reduction in concentration. Because of the presence of edema in all these cases, the possibility was considered that the low sodium values represented merely a dilution by retained fluid.

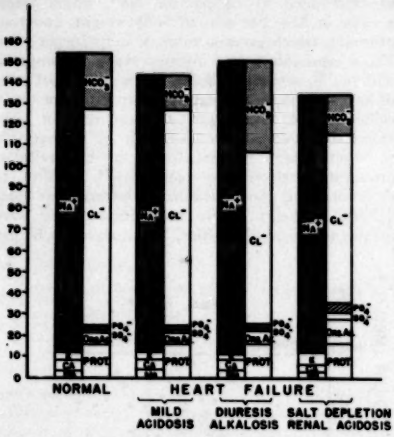

FIGURE 2. *Plasma Electrolyte Patterns in a Normal Person and in Three Patients with Congestive Heart Failure.*

However, dilution was not the sole explanation, for the concentration of chlorides in plasma was not similarly reduced except in 4 cases. In consequence of this greater reduction of sodium concentration as compared to chloride, there was a tendency to acidosis in most cases, although this was not pronounced (Fig. 2). These observations suggest that in heart failure the disturbance in water and electrolyte distribution involves the intracellular as well as extracellular compartments.

There is evidence that in heart failure sodium may pass through the cell membrane and potassium may leave the cell. This was suggested (though not proved) by the finding of a positive potassium balance in patients with heart failure who were receiving sodium and potassium salts.[37] Sinclair-Smith and associates[71] and Iseri and others[72] observed a positive potassium balance as patients recovered from heart failure and suggested that this indicated replacement of intracellular potassium lost as heart failure developed. Muscle biopsy specimens that indicated a rise in sodium concentration and a reduction in potassium concentration have been mentioned.[38] Difficulties arise because of the variable amount of interstitial tissue and water included with the muscle cells. Studies with radioactive potassium have disclosed a reduction in total body potassium in congestive heart failure, even though the concentration of potassium in the extracellular fluid is unaltered and the absolute amount of extracellular fluid is increased.[73] Despite this suggestive evidence, more direct proof is needed that potassium leaves the cells and that sodium enters the cells in heart failure. The possibility of determining the quantities of fluid in the various body water compartments and the possibility of following shifts of sodium and potassium by means of their radioactive isotopes afford promise of more direct measurement of the alterations in fluid and electrolytes within the important intracellular compartment.

One of the important corollaries of studies of electrolyte patterns in congestive heart failure is the frequent observation of a dissociation between sodium and chloride, especially in cases of heart failure. Because of former technical difficulties in sodium determinations it was customary to measure chloride concentrations in plasma and urine and to apply the results obtained to considerations of sodium metabolism as if the two electrolytes behaved in a quantitatively similar manner. This may lead to serious error in interpretation and management. Heart failure itself may be responsible for a dissociation in sodium and chloride metabolism because of differences in intracellular-extracellular exchanges or because of differences in renal ability to excrete these electrolytes. Furthermore, various therapeutic measures in heart failure and various complications or associated diseases may affect these electrolytes differently.

Diets extremely low in sodium tend to reduce the plasma sodium concentration (though only slightly), with virtually no effect on chloride. With such low-sodium diets the urinary output of sodium may vary from very low to minimal values, according to the degree of restriction of intake. On the other hand, the intake of chlorides, in combination with other cations, may be only moderately reduced by the low sodium intake; consequently the chloride output in the urine may be significantly higher than that of sodium. When the low-sodium diet is given in the form of the fruit-rice regimen of Kempner,[74] metabolism of the organic-acid anions may lead to high levels of bicarbonate, excessive elimination of potassium ion and hypochloremic alkalosis, usually of mild degree.[75]

Patients receiving ammonium chloride as a diuretic may develop a high plasma chloride relative to sodium and a tendency to acidosis. In such patients who are also receiving a very low sodium chloride diet, the determination of urinary chloride could not be used as a measure of urinary sodium concentration, for the latter may be minimal, whereas the chloride may be relatively high as a result of the ammonium-chloride medication.

Effect of Mercurial Diuretics

The plasma-electrolyte pattern in patients with heart failure may be substantially altered by repeated frequent mercurial injections. The diuresis obtained with mercurials results in a profuse excretion of sodium and chloride. However, as shown in Figure 3, the excretion of chloride is often high relative to sodium.[37] Although the sodium concentration in the excreted urine is usually at or somewhat below its concentration in plasma, the chloride concentration is usually equally high or higher and may exceed the concentration in plasma. Thus, with repeated diuresis there may be a reduction in the plasma chloride concentration, sometimes of serious degree, whereas the sodium concentration is virtually unaltered. The hypochloremia is associated with alkalosis and hypokalemia (Fig. 2).[76, 77] The hypokalemia appears to result from increased excretion of potassium following the administration of mercurial diuretics. A similar loss of potassium ions may result from protracted use of ammonium chloride. A corollary of the potassium depletion found in cases of heart failure, — particularly following the use of diuretics when combined with inadequate intake, — is the observation that digitalis-induced cardiac arrhythmias occur more frequently and that such arrhythmias may be promptly abolished by the administration of potassium salts.

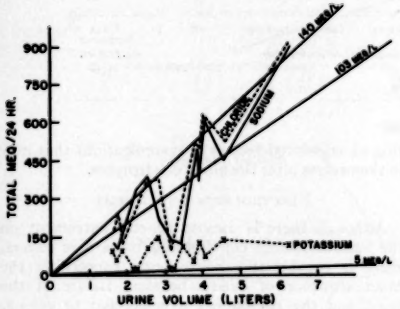

Figure 3. *Mercurial Diuresis and Urinary Electrolyte Excretion in Congestive Heart Failure.*

Table 5 shows electrolyte studies in a patient with congestive heart failure following mercurial diuresis. At the time of admission he had already received some mercurial diuretics. His electrolyte spectrum was essentially normal, but the chloride concentration was at the lower limit and the bicarbonate concentration was at the upper limit of normal. He was given four mercurial injections in the next six days, with only moderate diuresis. His plasma-electrolyte spectrum now showed a normal sodium, markedly diminished chlorides and an elevated bicarbonate, indicative of hypochloremic alkalosis. There was also a concomitant reduction in plasma potassium.

A similar example of hypochloremic alkalosis is seen in Table 6, which shows the plasma-electrolyte spectrum of a patient with advanced congestive heart failure who was responding poorly to mercurial diuretics after he had received numerous injections. He was stuporous, incontinent and sometimes irrational. A routine chloride determination was reported as showing a plasma chloride of 500 mg. per 100 cc. as sodium chloride. On this basis it was assumed that both his sodium and chloride were low, and an infusion of 5 per cent sodium chloride was recommended. However, a complete plasma-electrolyte spectrum disclosed that although the chloride concentration was extremely reduced the sodium concentration was normal. The disproportionate reduction in chloride was accompanied by a compensatory elevation in bicarbonate ion and alkalosis. The latter was denoted also by the high pH, suggesting that the hypochloremic alkalosis was only partially compensated.

Instead of sodium chloride infusions, which might have increased water retention, the patient was given ammonium chloride, with distinct improvement in his clinical state as well as in his electrolyte pattern. In some cases a more effective correction of the electrolyte pattern appeared to follow the administration of potassium as well as of

Table 5. *Hypochloremic Alkalosis in Heart Failure Following Mercurial Diuresis (Patient A. K.).*

	Sodium	Potassium	Chloride	Carbon Dioxide	Urea Nitrogen
	milliequivs./liter	*milliequivs./liter*	*milliequivs./liter*	*milliequivs./liter*	*mg./100 cc.*
Normal	135–143	4–5	97–105	24–29	12–20
7/14	140	4.4	98	29	45
7/20	139	3.7	79	33.5	50

chloride. Because of the deleterious effect of such electrolyte disturbances on renal function,[78,79] renal excretion of sodium and water in heart failure may be further impaired and contribute to intractable heart failure. With correction of the disturbed electrolyte pattern a more effective response to mercurial diuretics and other therapeutic measures may follow.

Effect of Sodium Depletion and of Renal and Pulmonary Disease

A reduction in both sodium and chloride has occurred occasionally in cardiac patients on a diet very low in sodium who were receiving frequent mercurial diuretics, and has been reported after the mechanical removal of edema fluid and ascites.[80] These patients disclosed evidence of rapid dehydration, with muscular cramps, azotemia and a shock-like syndrome, the so-called salt-depletion syndrome.[82-86] The spectrum in such cases may be similar to that seen in renal insufficiency (Fig. 2). Dramatic clinical improvement may follow the use of hypertonic sodium chloride in sufficient quantity to raise the plasma sodium concentration to normal. However, a moderate hyponatremia is common in the usual case of heart failure without the salt-depletion syndrome. In such cases, hyponatremia per se is not an indication for sodium therapy, which may intensify the heart failure. There is need for a clearer delineation of the salt-depletion syndrome and of the criteria for its diagnosis. It is uncertain whether the clinical picture is due to a rapid and severe reduction in cardiac output caused by a contraction in circulating plasma volume, to depletion in sodium ion per se, to a consequent lowering of osmotic pressure of extracellular fluid or to changes in cellular potassium or hydration.

In patients with *renal insufficiency* as well as heart failure, the retention of organic acids, phosphates and sulfates results in a reduction of both chloride and bicarbonate, whereas the sodium concentration may be normal or low.

Pulmonary insufficiency may lead to retention of carbon dioxide with a compensatory increase in plasma bicarbonate, which in turn might suggest the presence of alkalosis. Actually, acidosis is present, as can be determined by pH measurements. The administration of ammonium chloride based on the misinterpretation that the high carbon-dioxide combining power of the plasma denoted alkalosis would be improper, if not dangerous. Oxygen administered in high concentration to patients with congestive heart failure may result in a high plasma bicarbonate with acidosis. The oxygen, by diminishing the sensitivity of the respiratory center, may reduce the compensatory hyperventilation usually seen in heart failure and thus lead to retention of carbon dioxide.

These considerations should underline the importance of complete studies of the blood-electrolyte spectrum before therapeutic measures are undertaken to correct an isolated abnormality. Furthermore, the blood-electrolyte spectrum in cases of heart failure should be interpreted with consideration of associated factors or complications that may in themselves alter the blood electrolytes.

Table 6. *Ammonium Chloride in Hypochloremic Alkalosis (Patient A. L.).*

	Sodium	Potassium	Chloride	Carbon Dioxide	pH	Urea Nitrogen
	milliequiv./liter	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*		*mg./100 cc.*
Normal	135–143	4–5	97–105	24–29	7.38–7.43	12–20
1/10	139	3.8	81	32.5	7.53	12
1/18	134	4.0	90	30.9	7.47	20

Electrolytes and Edema

Although there is almost general agreement on the various factors contributing to cardiac edema, there is considerable controversy concerning the exact sequence of events between failure of the heart and the subsequent development of edema. A substantial portion of the disagreement has concerned the relative importance of sodium-water retention as compared with elevation of venous and capillary pressure and the order of occurrence of these two abnormalities in heart failure.

These two points of view are presented briefly in Figure 4, representing the backward-failure and forward-failure hypotheses.[81-86]

Heart failure is associated with a reduction in cardiac output, with a concomitant elevation of diastolic pressure in the failing chamber and also with an elevation of the hydrostatic pressure in the veins and capillaries leading to the failing chamber.[87-91] Considered from the venous side, the elevated capillary pressure exceeds the colloid osmotic pressure of plasma proteins (which is about 30 cm. of water) and leads to transudation of fluid into the interstitial compartment and eventually to edema.[92] However, such transudation should cause a reduction in plasma volume, whereas the plasma volume is actually increased in congestive heart failure. Secondly, transudation of the entire plasma volume would not suffice to produce the vast augmentation of interstitial fluid volume necessary to produce visible edema, as was shown in Table 1. Further, such loss of plasma volume would soon eliminate the elevated venous pressure.

It is therefore apparent that even if elevation of venous pressure were a primary event, neither the elevated venous pressure nor the edema could persist unless water (and sodium) were retained. Actual measurements denote that the retention of sodium and water not only restores the plasma volume but increases it,[91, 93] and in addition provides for the large quantity of extracellular fluid in the interstitial tissues. According to the backward-failure theory, the initial diminution in plasma volume or a rise in renal venous pressure stimulates renal retention of sodium chloride, the mechanism of which is uncertain — nor is it clear why such stimulation should lead to *more* than a restoration of the normal plasma volume.

The deficient cardiac output at the onset of heart failure is regarded as causing a reduction in blood flow to the kidney as well as to other organs concerned with sodium and water metabolism. This results in a retention of sodium and water, with consequent hypervolemia and edema. Actually, this concept is supported by catheterization studies that reveal a reduction in cardiac output and renal blood flow in heart failure,[92] and by other studies that disclose a reduction in glomerular filtration[91, 95] and a probable increase in tubular reabsorption of sodium.[96] In short, the reduced cardiac output and renal blood flow are represented as responsible for disturbances in renal dynamics, which result in sodium and water retention.

However, if one accepts this sequence of events, it seems necessary to suppose that the retained fluid must first be incorporated in the circulating plasma. Its subsequent transudation into the interstitial tissues may be due to reduction in colloid osmotic pressure caused by dilution of plasma protein. More likely, however, according to the actual findings in heart failure, such transudation is due to an elevation in venocapillary pressure, that is, to an increased hydrostatic-filtration pressure within the capillaries. It seems that if sodium-water retention is the earlier event in the production of edema an elevation of venous pressure is a necessary intermediate, even if only transiently, until equilibrium is established between intravascular and extravascular fluid and electrolytes.

I previously indicated that neither cardiac edema nor the elevated venous pressure of congestive heart failure could persist without retention of large quantities of sodium and water. However, the essential importance of an elevated venous pressure in cardiac edema may also be indicated. In cases of left-sided heart failure in which the venous pressure in the systemic circulation is normal, there is no peripheral edema. However, edema of the pulmonary tissues may occur in such cases in which

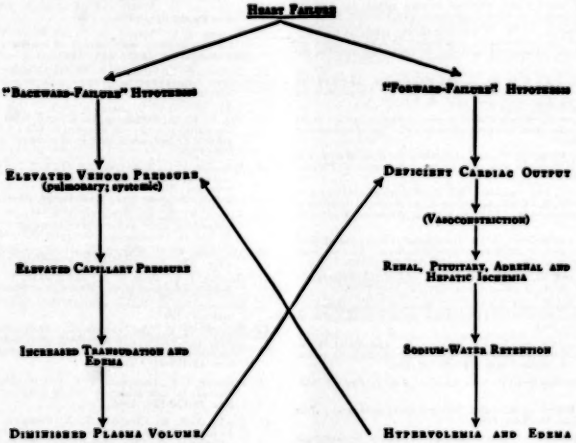

Figure 4.

the pulmonary venocapillary pressure is elevated. On the other hand, peripheral edema occurs commonly in right-sided heart failure, in which the systemic pressure is elevated either at rest or under the stress of an increased venous return. Furthermore, the edema is localized in the lower extremities if the patient is upright or in the sacrum if he is recumbent; that is, the edema occurs in those areas where gravity tends to exaggerate the elevated venous pressure of heart failure.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 37471

PRESENTATION OF CASE

A fifty-nine-year-old man entered the hospital because of painful swelling of the arms.

One month before admission on rising from bed in the morning he noticed swelling and weakness of both arms that was sufficient to prevent him from washing his face and from shaving. He felt otherwise well. The swelling was confined initially to the antecubital areas. Pain was present at the sites of swelling and radiated into the shoulders and forearms. The swelling increased and extended, more on the right, finally to include within two inches the entire arms from shoulders to fingers. Two weeks before admission he entered another hospital. Erythema was present on the right wrist and on the medial aspect of the right arm. He was febrile. An x-ray film of the chest showed diffuse linear infiltration but no enlarged mediastinal shadow. There was hypertrophic arthritis of the fourth, fifth and sixth cervical vertebras. Venograms of the right arm showed patent axillary and subclavian veins. A biopsy of skin and muscle showed no specific pathology. Urinalysis was negative. Blood sugars varied from 140 to 180 mg. per 100 cc. The cerebrospinal fluid was xanthochromic and contained 163 mg. per 100 cc. of protein. The electrocardiogram showed right-bundle-branch block. He was transferred to this hospital.

The patient had had mild diabetes for years and had been taking 5 units of protamine zinc insulin daily.

On examination the patient was emaciated, with signs of recent weight loss. There was slight tenderness over the occiput, but no abnormalities were palpable. There was marked pitting edema of both upper extremities, more marked on the right, reaching from the fingers to the shoulders. The swelling was tender on deep pressure. There was diminished pin-prick sensation in the upper extremities. The muscles of the arms were weak, and the deep tendon reflexes were unobtainable. No trophic changes were seen. There were several small nontender nodes in the right axilla. The legs were thin and atrophied. The knee jerks were absent; the ankle jerks were normal. The lungs showed decreased tactile fremitus and sticky rales in both bases, more marked on the left. The heart was not remarkable.

The temperature was 98.6°F., the pulse 90 and the respirations 30. The blood pressure was 150 systolic, 70 diastolic (left arm) and 180 systolic, 80 diastolic (right arm).

The urine was normal except for a + sugar reaction. Examination of the blood showed a white-cell count of 15,900 with 89 per cent neutrophils. The sedimentation rate was 0.5 mm. per minute. The fasting blood sugar was 133 mg., the nonprotein nitrogen 28 mg., the serum albumin 2.8 gm., the globulin 2.16 gm. and the cholesterol 197 mg. per 100 cc. The basal metabolic rate was + 10 per cent. The stools were guaiac negative. A twenty-four-hour urine specimen showed 340 mg. of creatinine and 235 mg. of creatine. The spinal-fluid findings were normal, the protein being 22 mg. per 100 cc. An electrocardiogram demonstrated a right-bundle-branch block. Electromyelograms were done on all the muscles of the body; frequent spontaneous aperiodic spikes were present in the triceps, extensor carpi and radialis muscles. X-ray examination of the chest showed a density at the right apex with destruction of the vertebral end of the fourth rib. A gastrointestinal series, barium-enema examination and x-ray films of the bones of the upper extremities demonstrated no abnormality.

While in the hospital the patient complained of marked pain in the area of the back between the scapulas and the vertebral column. A questionable area of slight swelling was present in this location. The patient was treated with hot applications to his back, with aspirin, and with a highly nutritional diet. He was afebrile. There was slight symptomatic improvement; the swelling of the arms subsided partially. He was discharged after five weeks in the hospital.

Second admission (one month later). For two weeks the patient did well; his appetite improved and he gained weight. He was ambulatory and relatively free of pain. Ten days before readmission pain in his throat appeared and swallowing became difficult. He developed a cough productive of several spoonfuls of thick yellow material. There was occasional dull anterior-right-chest pain, not related to breathing, which he thought was related to the right-upper-back pain. Five days before admission he awoke with pain and swelling in both upper extremities extending from the shoulders to the wrists. A rash suddenly appeared around the mouth. Strength decreased and the skin of the ab-

domen felt tight. Several small nontender nodules appeared on the forehead. The legs became swollen and the arms very tender.

On examination three small nontender nodules were present on the forehead. The face was slightly swollen, and there was an erythematous circumoral rash. The skin over the chest and abdomen was tight. Hard indurated swelling was present in both upper extremities from the shoulders to the wrists. The muscles of the thighs and arms were generally tender. On the ventrum of the penis there was a superficial indurated abrasion with phimosis of the foreskin. Multiple fine and a few coarse rales were heard over both lungs posteriorly. Examination of the mouth, pharynx and larynx showed no evidence of palatal weakness. The gag reflex was normal. The vocal cords and arytenoids moved well.

The temperature was 99°F., the pulse 100 and the respirations 20. The blood pressure was 140 systolic, 70 diastolic.

Chest roentgenograms demonstrated no significant change since the previous examination, the density at the apex appearing unchanged. A barium swallow passed readily down the esophagus.

The patient developed fever and had great difficulty in swallowing and in raising sputum, which was purulent. The temperature reached a maximum of 102°F. on the sixth hospital day. An x-ray film of the chest now showed mottled, irregular areas of increased density throughout the right lung and elevation of the right leaf of the diaphragm. Cultures of the sputum were negative. There was no response to penicillin or digitoxin, and the patient died on the eighth hospital day.

Differential Diagnosis

Dr. Robert L. Berg*: To summarize the evidence, this patient had a fatal generalized disease, affecting most tissue and organ systems of the body, that was most severe in the muscles, skin and lungs. Its precipitating symptom was swelling. In arriving at a diagnosis, it is convenient to consider the edema as a base around which to center the discussion. What abnormalities produce edema? They may be described under three headings: increased filtration pressure, increased capillary permeability and decreased osmotic pressure. The serum protein was not low enough in this patient to produce edema, so the explanation must be found in one of the first two factors. Inasmuch as the swelling was at first limited to the arms, a satisfactory explanation must indicate localized reasons for edema formation.

Local increases in filtration pressure may be produced by arteriolar dilatation, inactivity, dependency or venous obstruction. Only the last is probable in this patient and would presumably be due to a tumor. A tumor that could produce obstruction of the veins to both arms without causing obstruction to the head would have to be multiple; to explain the later involvement of the legs, one must postulate another lesion blocking the veins from the legs. Lymphoma might develop in this way and must be considered as a possibility.

Local increases in capillary permeability may be due to many disorders but are most commonly due to infectious diseases and to the spectrum of pathologic conditions called connective-tissue disease. It seems to me, then, that in the differential diagnosis must be included lymphoma, infection and some connective-tissue disease, which by the nature of its distribution and characteristics would be dermatomyositis. I shall discuss the case from the point of view of these three diseases.

Lymphoma could cause obstruction, but there are few arguments to support the notion that the edema was due to obstruction. It is true that it was found at first to be a pitting edema; this may happen with venous stasis. However, I have to account for the fact that there was improvement between the first attack and the second and fatal recurrence. There is a remote possibility that the x-ray studies may have so affected a very radiosensitive lymphoma that there was enough improvement to allow a loss of the edema. Also the fact that it was painful and tender, particularly on deep pressure, does not fit well with edema due to venous stasis. It is hard to explain both the improvement and the subsequent recurrence on that basis. That is more the sort of thing one sees with a connective-tissue disorder; the very widespread nature of this illness makes both malignant obstruction and infection somewhat difficult to accept. With only a few exceptions dermatomyositis would fit very nicely.

Dermatomyositis characteristically causes more swelling and involvement of the upper extremities than of the lower extremities, and it is very hard to make the other diagnoses fit that particular finding. The evidences of muscular involvement are characteristic: weakness, pain, tenderness over the occiput, midscapular distress, dysphagia and the apparent paralysis of the right diaphragm. As far as the skin is concerned, the erythema, rash and tight skin fit well with a diagnosis of dermatomyositis. The nontender nodules on the forehead and forearm may have been calcified deposits, such as are sometimes seen in this disease. The major system changes, the loss of sensation (pinprick in this case) and the loss of tendon reflexes all are to be anticipated. I am at a loss to explain the findings in the spinal fluid. As far as I know it is not common to find parenchymal brain involvement, but hemorrhagic vesicles sometimes appear in the skin and elsewhere, and I suppose one could postulate there was some such disorder in the central nervous system. It later cleared.

I am disturbed about the lungs. The lesion in the apex, which did not change between the first and

*Assistant in medicine, Massachusetts General Hospital.

second admissions, suggests an old infection rather than tumor, which should have progressed. This may have been the residual of an old tuberculous infection. The linear infiltration, however, that was present on the first admission is consistent with connective-tissue disease.

The rib lesion can be adequately explained only as a malignancy, I suppose. Lymphomas produce rib lesions in a relatively high percentage of cases. Because the rest of the story is so much more characteristic of the connective-tissue group of diseases, I am forced to disregard the rib lesion. Maybe the patient had two disorders. The rib lesion may have been a separate disease that was related to the lesion in the right apex. If that was a malignant lesion, it is queer that it had not progressed between the first and second admissions. I shall leave it at that, but I am not happy about it.

A slightly elevated basal metabolic rate fits with any one of these diseases. The diabetes is an unrelated finding. The right-bundle-branch block could be related to dermatomyositis, but in view of the hypertension and diabetes it indicates coronary-artery disease.

May I see the x-ray films?

Dr. Joseph Hanelin: These cover a period of over two months. In all the films there is visible a homogeneous area of increased density at the right apex and a localized zone of bone destruction in the adjacent portion of the right fourth rib posteriorly. This has the appearance of a malignant process.

Dr. Berg: Could it be osteoporosis?

Dr. Hanelin: No.

Dr. Berg: This apical lesion is in very close proximity to the rib lesion.

Dr. Hanelin: Yes; the linear streaking visible in both lungs could represent a manifestation of dermatomyositis. Other films that we have of the spine and shoulder are not contributory.

Dr. Berg: In view of this last impressive evidence, I would have to say that there appears to have been a lesion in the lung, presumably malignant, and that in addition the patient had something else. In this case the nontender nodules that appeared over the forehead might well have been metastases. That forces me into the position of having to make two diagnoses, dermatomyositis and carcinoma of the lung with extension into the rib.

A Physician: In dermatomyositis, what is found in the electromyogram?

Dr. Berg: I do not know. I was going on the basis that with destruction of muscle there may be spontaneous spiking.

A Physician: This sounds like fibrillations of nervous origin, and for that reason I would not think of myositis or muscular disease.

Dr. Berg: Fibrillations may occur in rheumatoid arthritis; I do not know about dermatomyositis.

Dr. F. Dennette Adams: I know of no form of malignant disease that would give such diffuse symptoms except perhaps multiple myeloma. The nodules found on the head might suggest myeloma, but the blood serum globulin was low. Dr. Berg's diagnosis is much more tenable. Were skull films made?

Dr. Hanelin: The portion of the skull included in the cervical-spine films appears normal. One further point: The actual amount of exposure to x-rays during diagnostic procedures is generally small, and its effect is further lessened by being protracted over a period of time. It is not enough to affect a lymphoma.

Dr. Berg: Even with fluoroscopy?

Dr. Hanelin: The patients do not receive much.

Dr. Adams: How many r do they get?

Dr. Hanelin: At the Massachusetts General Hospital filtration of the central beam has been adjusted so that not over 10 r per minute reaches the patient. We rarely fluoroscope more than five minutes — ordinarily not more than two or three. The exposed area will vary during the examination and is kept small.

Clinical Diagnosis

Dermatomyositis.
?Pulmonary tuberculosis.

Dr. Berg's Diagnoses

Dermatomyositis.
Carcinoma of the lung with extension into rib.

Anatomical Diagnoses

Dermatomyositis.
Squamous-cell carcinoma of lung with extension to pleura and rib.
Bronchopneumonia.
Pulmonary fibrosis.
Coronary sclerosis.

Pathological Discussion

Dr. David Kahn: The physicians who cared for this patient had the advantage of a skin and muscle biopsy. This showed focal degenerative changes in some of the muscle fibers with some scattered round-cell infiltration. It was compatible with, but not diagnostic of, dermatomyositis, or one of the closely related so-called collagen diseases. At autopsy there were circumscribed skin lesions over both cheeks. There was hazy subcutaneous edema of all four extremities. The skeletal muscles were thin and atrophic and much paler in color than normal. Histologic examination of the skeletal muscle showed a picture quite typical of dermatomyositis. The muscle fibers were atrophic, and there were scattered areas of definite muscle degeneration. This varied from very early changes, with only a loss of striation of the muscle fibers, to actual necrosis with fragmentation of fibers. In some sections the change was focal; in others it was widespread. In relation to most of these areas

there was a fairly heavy inflammatory infiltrate consisting of lymphocytes, monocytes and plasma cells. There was marked fibrosis throughout the muscles. The vessel changes were minimal; the walls appeared to be slightly thickened, but there was no fibrinoid necrosis. Sections of the skin showed a rather nonspecific change, as is often the case in this disease. There was atrophy of the epidermis, edema of the superficial corium and marked fibrosis of the deeper corium and subcutaneous fat; there were no vascular changes, fibrinoid necrosis or inflammatory cells. We did not find any lesion in the internal viscera that we could definitely attribute to dermatomyositis. Lesions have been described in cardiac muscle, intestinal tract, lungs, synovia and adipose tissue, but none were present in this patient.

The lesion in the lung was a bronchogenic carcinoma. It was in the posterior apical segment and measured 5 by 4 by 2 cm. in diameter. There was diffuse infiltration throughout the whole segment, with extension through the pleura and infiltration of the posterior chest wall at the level of the fourth rib; the proximal 4 cm. of this rib was infiltrated by tumor and almost totally destroyed. We were unable to identify the bronchus from which the tumor had arisen. Microscopically it was a squamous-cell carcinoma. The pulmonary lymph nodes were not involved, and there were no distant metastases.

DR. HANELIN: Were there any diffuse pulmonary changes?

DR. KAHN: The lungs were firm and indurated. They weighed 1700 gm. Microscopically there was a severe bronchopneumonia throughout all lobes. In addition, there was a moderate degree of nonspecific pulmonary fibrosis.

DR. BERG: What was the heart like?

DR. KAHN: There was a moderate degree of coronary sclerosis. It was not enlarged. There was a small myxoma of the pulmonary valve, which we considered an incidental finding rather than one related to the dermatomyositis. The brain and spinal cord were normal.

CASE 37472

PRESENTATION OF CASE

A fifty-five-year-old woman entered the hospital because of hematuria.

Ten days before admission the patient first noted hematuria associated with frequency and pain in the left flank. Three days later she entered another hospital, where x-ray films of the abdomen were said to reveal no "stones." Following a bladder irrigation the bleeding ceased for about one week and she was discharged from the hospital. The day following discharge bright-red blood and some clots were passed, accompanied by pain in the left side.

There was no history of recent weight loss. Thirteen years previously a hysterectomy had been performed for the removal of a "benign tumor."

On physical examination there was a questionable fullness in the region of the left kidney. The remainder of the examination was negative.

The temperature was 99.6°F., the pulse and respirations were normal and the blood pressure was 135 systolic, 80 diastolic.

Examination of the blood disclosed a hemoglobin of 10.5 gm., a red-cell count of 3,280,000 and a white-cell count of 11,900. The urine was cloudy red in color, had a specific gravity of 1.020 and gave a ++++ test for albumin; the sediment was loaded with red cells. The serum nonprotein nitrogen was 29 mg. per 100 cc.; the Hinton test was negative.

An intravenous pyelogram on the day following admission demonstrated kidneys of normal size and shape. A normal kidney pelvis and ureter were visible on the right. During a 45-minute period no excretion took place on the left. The urinary bladder contained a large filling defect. (Cystoscopy was negative.) A left retrograde pyelogram showed the lower calyx pressed on and displaced upward by an approximately round mass (Fig. 1). On the periphery of the mass there were small areas of calcification. The upper ureter was displaced medially by the mass.

Urine taken on the third hospital day by catheter from the left ureter was loaded with red cells and gave no growth on culture.

On the fourth day the patient was given a transfusion and an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. WALTER S. KERR, JR.*: A fifty-five-year-old woman, ten days before entering this hospital, noted hematuria associated with pain in the left flank and with frequency. The bleeding persisted for approximately three days, stopped for about one week and then recurred. Again, it was accompanied by pain

*Assistant in urology, Massachusetts General Hospital.

in the left side. The patient had noted no weight loss or previous symptoms referable to the urinary system.

One examiner noted a questionable fullness in the left flank. Otherwise the physical examination was negative. Cystoscopy was negative and a retrograde pyelogram showed a "large mass in the region of the lower pole of the left kidney." Laboratory

FIGURE 1.

studies revealed the expected anemia and a urine loaded with blood.

Thus, I am faced with the problem of deciding the nature of a large mass in the lower pole of the left kidney of a fifty-five-year-old woman who has had severe hematuria accompanied by left-flank pain on two occasions in the past ten days.

Dr. McCort, would you kindly discuss the x-ray findings?

DR. JAMES J. MCCORT: The intravenous pyelogram is not available. We have one film taken during the retrograde pyelography. The catheter is seen in the left ureter. After the retrograde injection of dye, a large soft-tissue mass in the lower pole of the left kidney is visualized (Fig. 1). There is a suggestion of a slight flecky calcification in the periphery of this soft-tissue mass. The inferior calyx is not visualized. Flattening and upward displacement of the middle calyx and pelvis with some intraluminal protrusion of the mass into the left kidney pelvis is apparent. Whether this represents blood clot or tumor extension cannot be determined. There is also displacement of the upper third of the left ureter toward the midline. The psoas muscles are symmetrical. The visualized bones show no abnormality.

DR. KERR: The x-ray appearance of the lower pole of the left kidney in this case could be caused by a number of tumors, most of them unlikely. Solid retroperitoneal tumors such as lipomas, fibrosarcomas and their variations have on occasion caused the calyceal and pelvic pattern noted and have appeared to be part of the kidney. Usually, however, retroperitoneal tumors, if they affect the kidney at all, only cause displacement, without changes in the calyceal pattern.

Rare tumors arising in the kidney, such as solid benign tumors, teratoid tumors and hamartomas, are to be thought of only from the point of view of completeness. Carcinoma of the kidney pelvis will have to be mentioned in passing; these tumors usually cause hematuria before they become as large as this mass. Carcinomas of the kidney pelvis are more likely to give a positive Papanicolaou stain than renal-cell carcinomas, which originate in the cortex of the kidney. A perinephritic abscess is a remote consideration in view of the white-cell count and the history.

A solitary cyst and a renal-cell carcinoma (hypernephroma) are the most likely bets in this particular case. They are the most common kidney masses in adults. The x-ray appearance of this mass could be caused by either a cyst or a hypernephroma. As Dr. McCort has pointed out, there is calcification in the periphery of the mass. In my experience calcification is more common in renal-cell carcinomas than in cysts. Arteriograms are said to be helpful in differentiating these two lesions. However, the evidence they produce is not sufficient for me to decide not to operate — especially when tumors may occasionally occur within cysts. Medial displacement of the upper portion of the ureter is the last of the x-ray findings to be discussed. Such displacement is not caused as often by cysts as by tumors or large metastatic nodes.

Renal-cell carcinomas not infrequently metastasize or reach palpable size without causing hematuria, because they arise in the cortex of the kidney. However, they do bleed more frequently than cysts. The amount of hematuria in this case was sufficient to cause clots and a red-cell count of 3,280,000. I have not seen a cyst bleed to this extent. The left-flank pain accompanying the hematuria could be caused by bleeding into the mass, bleeding into the pelvis of the kidney or bleeding from the mass into the surrounding tissue. I imagine it was due to bleeding into the mass, for the pain apparently did not persist throughout the period of hematuria, as it might have done if caused by clots passing down the ureter. Palpation of cysts and hypernephromas is often possible. Occasionally a cyst will be decidedly soft and compressible, or a tumor will be nodular. Usually, however, palpation does not aid in deciding between them.

Before ending this discussion, I should like to emphasize that in spite of the information one gains from cystoscopic examination, Papanicolaou stain, pyelograms, perirenal air insufflations, arteriograms and other studies, the nature of many masses of the kidney can be determined only by visualizing the lesion. Unless there are adequate reasons for not operating there is only one course to follow — and that is to explore the kidney.

Clinical Diagnosis

Tumor of kidney.

Dr. Kerr's Diagnosis

Renal-cell carcinoma.

Anatomical Diagnosis

Hematoma of peripelvic fat with pressure necrosis of surrounding fat and kidney.

Pathological Discussion

Dr. Robert E. Scully: At operation the surgeon encountered a mass occupying the lower hilus and inferior pole of the left kidney. In the belief that this was neoplastic, a nephrectomy was performed. On sectioning, the operative specimen proved to be only clotted blood surrounded by an irregular rim of soft, yellow necrotic tissue. The entire lesion measured 7 cm. in diameter and occupied both peripelvic fat and adjacent renal parenchyma; the pelvis and ureter were displaced medially. Microscopical examination disclosed organizing hemorrhage and necrosis of fat and renal parenchyma. The necrosis appeared by its peripheral localization to be a pressure phenomenon. Numerous sections were taken in an attempt to elucidate the pathogenesis of the hemorrhage. No lesions were found in the arteries except for a rather severe intimal fibrosis and hyalinization. Several veins of medium size that lay in the hilus at the outskirts of the lesion showed areas of fibrinoid necrosis, and a few smaller ones contained organizing thrombi. However, we regarded these changes as being secondary to the necrosis and not causative lesions.

A Physician: Perirenal hemorrhage has been described in periarteritis nodosa; in view of the vascular lesions you mention, I wonder if the hemorrhage in this case may not have been the earliest manifestation of some generalized vascular disease.

Dr. Scully: I do not believe so. In a follow-up letter received from the patient some four and a half years after operation, she stated: "I am in good health and have not been in bed a day since I left the hospital."

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SPEAKING OF THANKSGIVING

IT is interesting as a purely speculative exercise to try to strike a trial balance, occasionally, of the debits and credits that are accumulating on the books in which mankind might be supposed to keep its imaginary accounts.

The present season of the year, when this indebtedness to a divine providence is expected at least to be acknowledged, is as good a time as any for such an accounting, however fanciful it may seem. A curious consistency about Thanksgiving, however, makes it customary to recognize only those impacts on life for which man should be thankful, a discreet silence being maintained about the ills that no stretch of the imagination can convert into blessings.

In material things the average American can still be thankful for food, fuel, clothing and shelter, of average quality and in reasonable quantity, if not in price. The people of this country as a whole, with the medical profession in the lead because it has a better understanding of the problem, may also be thankful that free enterprise still operates in medical practice as in other matters, with constant efforts being made to improve the distribution as well as the quality of medical care.

Socialism, even to the extent of communism (meaning true communism — not the type of dictatorship that passes for it in some parts of the world), may represent in principle the ideal pattern of organized living. The incontrovertible fact that disqualifies it in practice is that it must be administered by ordinary human beings.

If the strength of a nation, as has been fondly quoted, lies in the hearts of its people, then its weaknesses must spring from their heads. Only those creatures that cannot think, — the bees and the ants and the wasps, — have been able to organize and conduct perfect communistic societies — completely equitable and completely ruthless.

Among the inescapable facts of life for which thanks need hardly be expressed are the devious ways by which democracy attempts to reach its often ill-defined goals, and sometimes the very guides that it selects to lead it on its way. An acceptance of the tenet that man is born into trouble as the sparks fly upward makes it occasionally seem as if a considerable conflagration of incendiary origin were raging.

And yet, despite the corruption that appears so often to be so universal, the final balance can probably be entered in black ink, at least by the moderately optimistic. Thanks may still be given that, muddleheaded as men are in the aggregate, there remains a working minority of persons with intelligence and courage and ideals, who think that they were born to set things right.

TRAINED SEALS

AGAIN a reminder is in order that the annual Christmas Seal Sale of the National Tuberculosis Association will be one of the major campaigns of

the season, having begun on November 19 to continue until Christmas.

The methods of tuberculosis control may have changed as science has progressed and the epidemiology of the disease has become modernized; the need for continuing the fight remains constant, and financial support in the battle is necessary as never before.

Tuberculosis still remains a major health problem, still causing more deaths, even in the United States, than all other infectious diseases combined. Significant is the fact that the decline in the death rate from tuberculosis has not been matched by a decrease in the number of new cases; treatment has made more effective progress than has control of the spread of the infection.

To realize the continuing importance of this problem the fact must be appreciated that as recently as 1949, — the latest year for which complete figures are available, — 40,000 persons in the United States died of tuberculosis — a rate of more than 100 a day, or 1 every thirteen minutes. Estimates of the worldwide toll taken by the disease are placed at nearly 5,000,000 a year.

These figures indicate the immensity of the tuberculosis problem but need suggest no element of hopelessness, for in the last fifty years the death rate has shown an 85 per cent decline. This decline is an indication of what can be accomplished with any plague, no matter how serious, if it can be attacked with understanding and if the conditions that promote its spread are ameliorated.

In the specific attack on tuberculosis, funds are constantly needed and the Christmas Seal Sale is one of the most effective means of obtaining them. These are the seals that are so trained that they can enter every home and ride on every letter and package that passes through the mails from now until Christmas!

"C.P.C" — CLINICAL ANALYSIS OR GUESSING GAME?

In one of the recent case records of the Massachusetts General Hospital testimony is published on a matter that must have been running through the minds of many physicians for years. The point was made that the clinicopathological conference is occasionally a guessing game rather than a concerted analysis of a clinical case by all specialists concerned with its proper handling. The protagonist of this viewpoint was Dr. Edward D. Churchill, called upon to diagnose a case of pulmonary disease. At home in a field where he is an acknowledged authority, he said: "I dislike discussing this case, because I see so much harm done these days from using clinicopathological-conference technics on living patients before the course [of treatment] . . .is definitely charted. . .I know I do not know what this [x-ray] shadow represents. . .Too much emphasis is placed on making guesses. . .instead of arriving at a clear-cut decision as to what course of action is advisable. There is no train of logical reasoning or experience that might enable anyone to make a preoperative diagnosis in this case. With a lump that is accessible to palpation, certain physical signs may help determine its nature — hardness, firmness, mobility and so forth. One cannot palpate a shadow."

Most readers will concur with Dr. Churchill that the point of the case discussion is not the expert's best guess but how the pathologic findings explain the clinical course and symptoms. Knowing the real diagnosis, living sequences can be reconstructed in hindsight. The die has already been cast and the lifeless tissues have come under the knife and the microtome. The diagnosis that someone else made has determined the course of the patient's therapy, a matter no longer of opinion but of record. The patient's own physician is the appropriate person to discuss the clinical and operative course. The pathologist takes up where the clinician leaves off — at the terminal and terminated illness. He may be able to explain processes that were inexplicable during life. The instructive aspect of the diagnostic problem is not a correct answer by a quiz kid but analysis of the obstacles that confronted the physician who actually handled the case. Could the diagnosis of cancer have been made earlier? Could bronchoscopy or bronchial cell washings have helped? How did the tumor arise? Could it have been prevented? Should it have been treated differently? The patient's own physician may or may not — indeed he probably does not — know all the correct answers. That is of little moment.

What is of greater importance is that he and perhaps one or two house officers are the only ones who had the authentic "feel" of the case — the appreciation of the degree of the patient's pallor, the odor of her breath, the precise color of the blood-tinged sputum, the dryness of the parched tongue, the querulous reaction to her illness and the psychosomatic background for this reaction. The family physician is the person to discuss the protocol, to reconstruct the downhill progress, to analyze his mistakes so that others may profit, to explain his successes so that others may learn.

To be confronted with a paper case is to be presented with a ghost — a ghost who doesn't really suffer, who can't clarify the details of her illness, such as the subtle shift in chest discomfort and dyspnea, when the hemoptysis first occurred, what it was like, why the patient consulted the first doctor, and what the first doctor thought. Small wonder that Dr. Churchill, who saw only the ghost, guessed that the tumor was benign when the pathologist knew that it would turn out to be malignant — that it did not lie within the lung, whereas the surgeon had already found it widely invading the lung substance.

To see the top brass thrown to the lions while the spectators watch hopefully for blood is not without its rewarding features — especially if the brass happens to slip while the lions are in midair. Dr. Churchill likened himself not to a martyred centurion but to Casey at the bat — Tallulah Bankhead's version. When his wife asked Casey what had happened, all he could say was: "I don't know; I just don't know."

Both the strike-outs and the home runs are worth waiting for.

Some readers will remember a day, years ago, when the late Soma Weiss had just made such a magnificent guess (periarteritis nodosa) that even before it had been confirmed, the rafters — if there are any rafters over the auditorium at Allen Street — rang with applause. To revert to Casey at the bat, it was one of those fateful moments when a fence-clearing line drive has been slammed out uncomfortably close to the flagpole and it is not yet clear whether a home run or a foul ball has been hit. Dr. Weiss remained standing, awaiting the umpire's decision; he stilled the applause with an imperious gesture, remarking: "In Hungary we have a saying: Praise the day after sunset."

Entertaining as the guesses may be, the clinico-pathological conference is neither a sporting event nor a quiz program. Dr. Tracy Mallory, beloved umpire of many guessing games and exponent of biologic principles, summed up the modern objective in substantial agreement with Dr. Churchill: "Since Dr. Cabot's retirement the emphasis in clinico-pathological conferences has shifted from primary interest in diagnosis to explanation of how the demonstrated pathologic lesion or lesions explain the clinical course and symptoms. The latter may sometimes be a difficult task for the pathologist because the evidence is not always adequate." This is as it should be. The umpire is not an umpire at all; he is a member of the team.

History of the Mass. General Hospital. — N. I. Bowditch, Esq., is the author of one of the best printed volumes that we have seen, relating to the history of the best conducted hospital in the country.

Boston M. & S. J., *November 26, 1851*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

COVNER — Albert H. Covner, M.D., of Swampscott, died on October 27. He was in his fifty-first year.

Dr. Covner was graduated from Tufts College Medical School in 1924.

His widow and a son survive.

RAYNES — Myrton B. Raynes, M.D., of Melrose, died on November 7. He was in his eighty-fifth year.

Dr. Raynes received his degree from the University of Maryland College of Physicians and Surgeons in 1896.

His widow, a daughter, three sons, nine grandchildren and two great-grandchildren survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The December schedule for consultation clinics for Crippled Children in Massachusetts follows:

Orthopedic Clinics	Date	Clinic Consultant
Salem	December 3	Paul W. Hugenberger
Haverhill	December 5	William T. Green
Greenfield	December 6	Charles L. Sturdevant
Lowell	December 7	Albert H. Brewster
Lynn*	December 10	Daniel M. Killoran John J. Crowley
Gardner	December 11	Carter R. Rowe
Brockton	December 13	George W. Van Gorder
Springfield	December 18	Garry deN. Hough, Jr.
Pittsfield	December 19	Edward J. Coughlin, Jr.
Worcester	December 21	John W. O'Meara
Hyannis	December 27	Paul L. Norton
Fall River	December 31	David S. Grice
Rheumatic-Fever Clinics		**Dates**
North Reading		December 4, 11, 18
Fitchburg		December 5, 12, 19, 26
Plastic Clinics		**Consultant**
Eastern Massachusetts	Semi-monthly	Bradford Cannon
Western Massachusetts	Monthly	Joseph M. Baker

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Hospital.

BOOK REVIEWS

Paracelsus: Magic into Science. By Henry M. Pachter. 8°, cloth, 360 pp., with 11 illustrations. New York: Henry Schuman, Incorporated, 1951. $4.00.

An excellent biography of Paracelsus, the controversial Renaissance figure in medicine, has been provided by Dr. Pachter, who has done full justice to his subject. The book is the result of long research, with investigation of documentary material unavailable to earlier biographers. It is well written and interesting, and it presents a clear picture of the vivid life of Paracelsus. Illustrations accompanying the book are excellent, and in general the volume is extremely attractive. It can be highly recommended as an exceptional biography. Paracelsus should be remembered for his fight against orthodoxy, not for any particular treatment that he accomplished. Few of his formulas have stood the test of time, but his influence, widespread in his day, continued for many years after his death, and traces of it are evident even at the present time.

Henry R. Viets, M.D.

General Theory of Neuroses: Twenty-two lectures on the biology, psychoanalysis and psychohygiene of psychosomatic disorders. By Rudolf Brun, M.D. 8°, cloth, 468 pp., with 3 plates and 1 illustration. New York: International Universities Press, Incorporated, 1951. $10.00.

Professor Brun of Zurich has long been recognized as a leader in neurology and psychiatry. His lectures were first published in 19?? and achieved popularity in Europe in their original form. They had been given to physicians and students, not all of whom were students of medicine, at the University of Zurich for a number of years and covered the subject in a broad manner, considering such topics as psychosomatic relations and the neuroses, the theories of instinct and the mechanisms of symptom formation. These lectures, now translated into English, form a valuable contribution to the subject. Although somewhat general in character, they contain enough basic material to appeal to any physician interested in the care of this large group of patients. The lectures are based on a broad understanding of neurophysiology as well as of psychopathology. An adequate bibliography and index complete the volume. The arguments favoring the theory that an examination from a biologic point of view verifies Freud's most essential assumptions are the basis of Brun's presentation. Not all will agree with him, but nevertheless his lectures are thoughtful and provocative and well worth reading.

Henry R. Viets, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Eternal Eve: The history of gynecology and obstetrics. By Harvey Graham, M.D. 8°, cloth, 699 pp., with 20 illustrations, 20 plates and frontispiece. Garden City, New York: Doubleday and Company, Incorporated, 1951. $10.00.

Dr. Graham, the author of *The Story of Surgery*, has written a new volume on the history of gynecology and obstetrics. It is comprehensive in scope, dealing with the subject from the earliest times to the nineteenth century. The chapter on puerperal pestilence is well written; due credit is given both Dr. Holmes and Dr. Semmelweis for their part in the eradication of this disease. The text is well written, and there are indexes of personal names and subjects. The volume should be in all collections on the history of medicine.

Surgical Forum: Proceedings of the forum sessions, thirty-sixth clinical congress of the American College of Surgeons, Boston, Massachusetts, October, 1950. Owen H. Wangensteen, M.D., Chairman. 8°, cloth, with 248 illustrations and 87 tables. Philadelphia: W. B. Saunders Company, 1951. $10.00.

In this volume of transactions the subject matter comprises various papers on the lungs and esophagus, stomach, peritoneum, intestines and pancreas, liver and bile ducts, heart and vascular system, and neurosurgery. There are also sections on wounds and wound healing, metabolism and nutrition, transfusions, shock and hemorrhage, malignancy, endocrines, and anesthesia. All the papers are documented with short lists of references. There is a comprehensive index. The volume should be in all medical libraries.

Die Entzundungs-Bestrahlung. By Habil R. Glauner, Dr. Med., lecturer on roentgenology and x-ray therapy and chief, Division of Roentgenology, Marienhospital, Stuttgart. Second edition. 8°, cloth, 189 pp., with 17 illustrations and 10 tables. Stuttgart: Georg Thieme, 1951. DM 18.60. Distributed by Grune and Stratton, Incorporated, New York. $4.45.

This special monograph on the x-ray treatment of inflammations was first published in 1940. The text is divided into two parts, general and special. The first part discusses inflammation in general and the effects of the x-rays. The special part concerns the various organs and tissues of the body. There is a special chapter on tuberculosis. There is a bibliography of 11 pages, arranged by chapters, and a good subject index. The publication is excellent. The volume should be in all collections on the subject.

Leitfaden der Blutmorphologie: Manual of blood morphology: Précis de Morphologie Sanguine. By Lydia Schudel, Hämatologische laborantin der medizin, Universitätsklinik, Zurich. Seventh edition. 8°, paper, 51 pp., with 17 color plates. Stuttgart: Georg Thieme, 1951. DM 14.80. Distributed by Grune and Stratton, Incorporated, New York. $3.50.

This manual on blood tests was first published in 1936; the need of a seventh edition speaks well for the soundness of the book. The text and nomenclature have been revised to conform with modern viewpoints. All the illustrations have been newly drawn. The color work is excellent.

Studies in Pathology. Presented to Peter MacCallum. Edited by E. S. J. King, T. E. Lowe, and L. B. Cox. 8°, cloth, 350 pp., with 42 plates. Victoria, Australia: Melbourne University Press, 1950. $7.00.

This memorial volume presented to Professor MacCallum is the joint work of twenty-three of his students and associates. The various papers cover the whole field of pathology. There is a good index and lists of contributors and subscribers. The book is well published in every way and should be in all collections on pathology and of medical memorial volumes.

Hospital Staff and Office Manual. By T. M. Larkowski, M.D., professor of clinical surgery, Stritch School of Medicine, Loyola University, and A. R. Rosanova, M.D., clinical instructor, University of Illinois Medical School. 16°, cloth, 428 pp., with 48 illustrations. Great Neck, New York: Romaine Pierson, Incorporated, 1951. $5.00.

This condensed manual on diagnosis and treatment is well written and well published. It has a good index and should prove useful as a ready reference source.

NOTICES

THE BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The Boston City Hospital House Officers' Association announces the following programs in its Evening Lecture Series:

Tuesday, November 27 — "Periodic Disease," by Dr. Hobart A. Reimann, professor of medicine, Jefferson Medical College. Discussers: Drs. Chester S. Keefer and Maxwell Finland.

Tuesday, December 4 — "The Developmental Diagnosis of Infant Behavior: Its Role in Clinical Pediatrics and Child Psychiatry," by Dr. Arnold Gesell, director, Clinic of Child Development, Yale University School of Medicine. Discussers: Drs. J. LeRoy Conel and Randolph K. Byers.

Tuesday, December 11 — "Cardiovascular Visualization" by Dr. Charles T. Dotter, assistant professor of radiology, Cornell University Medical College. Discussers: Drs. Max Ritvo and Israel Steinberg.

These programs will be given at 7:00 p.m. in the New Cheever Amphitheatre of the Dowling Building of Boston City Hospital.

All interested persons are invited to attend.

FELLOWSHIPS IN INDUSTRIAL HEALTH

The Institute of Industrial Health of the University of Cincinnati will accept applications for a limited number of fellowships offered to qualified candidates who wish to pursue a graduate course of instruction in preparation for the practice of industrial medicine. Any registered physician who is a graduate of a Class A medical school and who has completed satisfactorily at least two years of training in a hospital accredited by the American Medical Association may apply. (Service in the Armed Forces or private practice may be substituted for one year of training.)

The course of instruction consists of a two-year period of intensive training in industrial medicine, followed by one year of practical experience under adequate supervision in industry. Candidates who complete satisfactorily the course of study will be awarded the degree of Doctor of Industrial Medicine.

During the first two years the stipends for the fellowship vary, in accordance with the marital status of the recipient, from $2100 to $3000. In the third year the candidate will be compensated for his service by the industry in which he is completing his training. Additional information may be obtained from the Institute of Industrial Health, College of Medicine, Eden and Bethesda, Cincinnati 19, Ohio.

NEW ENGLAND PEDIATRIC SOCIETY

The next meeting of the New England Pediatric Society will be held on Wednesday, December 12. A medical clinic will be held at 11:00 a.m. in the Main Amphitheatre, Peter Bent Brigham Hospital. The afternoon scientific session will be held at 2:15 p.m. in Amphitheatre C, Harvard Medical School. The evening meeting will be held at Longwood Towers, Brookline. A symposium on accidents in children will be presented.

THE AMERICAN COMMITTEE ON MATERNAL WELFARE, INC.

The Fifth American Congress on Obstetrics and Gynecology will be held in Cincinnati, Ohio, March 31 through April 4, 1952, at the Netherland Plaza Hotel.

Further information and registrations or reservations may be obtained by writing to Mr. Donald F. Richardson, Executive Secretary, American Committee on Maternal Welfare, 116 South Michigan, Chicago 3, Illinois.

ESSEX NORTH DISTRICT MEDICAL SOCIETY

The 111th winter meeting of the Essex North District Medical Society will be held on Wednesday, January 9, 1952, at the Pentucket Club, 111 Main Street, Haverhill. Dinner will be served promptly at 1:15 p.m., and will be followed by the regular business meeting.

The guest speaker will be Dr. Francis D. Moore, surgeon-in-chief, Peter Bent Brigham Hospital. His topic will be "Management of Burns."

THE SPRINGFIELD HOSPITAL

The educational program of the Springfield Hospital for the month of December is as follows:

Saturday, December 1.
9–10 a.m. Grand Surgical Rounds.
10 a.m.–12 m. Combined Medical-Surgical Grand Rounds with Panel Discussion on "Medical and Surgical Aspects of Peripheral Vascular Disease" in the Staff Conference Room.

Wednesday, December 5.
11 a.m.–12 m. Psychosomatic Medicine Conference in the Out Patient Department.

Saturday, December 8.
9–10 a.m. Surgical Grand Rounds.
10–11 a.m. Conference on Plastic Surgery by Dr. Joseph M. Baker in the Staff Conference Room.
11 a.m.–12 m. Clinicopathological Conference in the Staff Conference Room.

Wednesday, December 12.
11 a.m.–12 m. Psychosomatic Medicine Conference in the Out Patient Department.

Thursday, December 13.
12:15 p.m. Staff Meeting in the Staff Room.

Saturday, December 15.
9–10 a.m. Surgical Grand Rounds.
10–11 a.m. Pathology Conference in the Staff Conference Room by Dr. William Kaufman.
11 a.m.–12 m. Medical Death Review in the Staff Conference Room.

Tuesday, December 18.
8:30 p.m. Guest Speaker Conference in the Staff Conference Room on the subject "Demonstration of the Gull-Strand Slit-Lamp." (Department of Ophthalmology.)

Wednesday, December 19.
11 a.m.–12 m. Psychosomatic Medicine Conference in the Out Patient Department.

Saturday, December 22.
9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Surgical Conference in the Staff Conference Room.
11 a.m.–12 m. Surgical Death Review in the Staff Conference Room.

There will be no teaching conference between December 23, 1951, and January 4, 1952.

All physicians are cordially invited to the conferences, seminars and grand rounds listed above.

(*Notices concluded on page xi*)